THE CONFORMATION AND REGIOCHEMISTRY OF STERICALLY HINDERED AROMATIC METHOXY GROUPS

By

MONICA ANN WYSOCKI

Bachelor of Science

Cameron University

Lawton, Oklahoma

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THE CONFORMATION AND REGIOCHEMISTRY OF STERICALLY HINDERED AROMATIC METHOXY GROUPS

Thesis Approved:

E. J. Eisenbraun
Thesis Adviser

L. Speers

Elizabeth M. Holt

Elden C. Nelson

Norman N. Durham
Dean of the Graduate College

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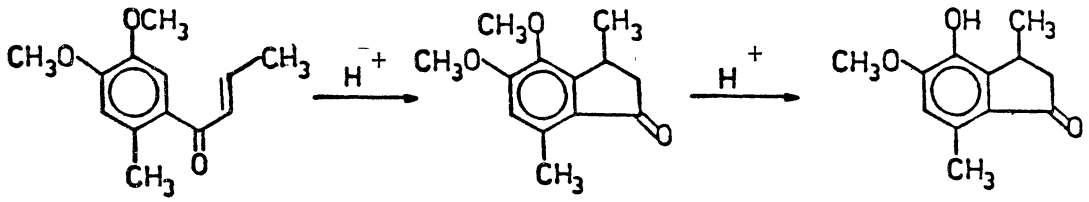
SYMBOLS AND ABBREVIATIONS

^{o}C	degree Centigrade	mL	milliliter
d	doublet	mm	millimeter
FT	Fourier transform	mol	mole
g	gram	mp	melting point
GC	gas chromatography	MS	mass spectrometry
h	hour	NMR	nuclear magnetic resonance
Hz	Hertz	o.d.	outside diameter
KHz	kiloHertz	p	pentet
L	liter	PPA	polyphosphoric acid
LAH	lithium aluminum hydride	ppm	parts per million
LC	liquid chromatography	q	quartet
lit	literature	s	singlet or second
M	molar	t	triplet
m	multiplet	TMS	tetramethylsilane
m/e	mass/electron charge	v	volume
MHz	megaHertz		

CHAPTER I

INTRODUCTION AND HISTORICAL

Interest in the reactivity of sterically hindered aromatic methoxy groups, that is, those flanked by two ortho substituents, was stimulated when it was noted that acid-catalyzed cyclization of 4',5'-dimethoxy-2-methyl-crotonophenone (1)[1,2a] resulted in demethylation of the more hindered methoxy group regiospecifically[3] to give 3,7-dimethyl-4-hydroxy-5-methoxy-1-indanone (3) via 2.[2a] To assist the reader, a glossary of structures is provided on pages 70-75.



1 2 3

This observation prompted an investigation into the demethylation of 3-alkyl-1,2-dimethoxybenzenes with Lewis acids, such as boron tribromide and iodotrimethylsilane, to determine whether the specificity of cleavage of the sterically crowded methoxy group was general in nature. The results are presented in Table I.[2] Treatment of

TABLE I

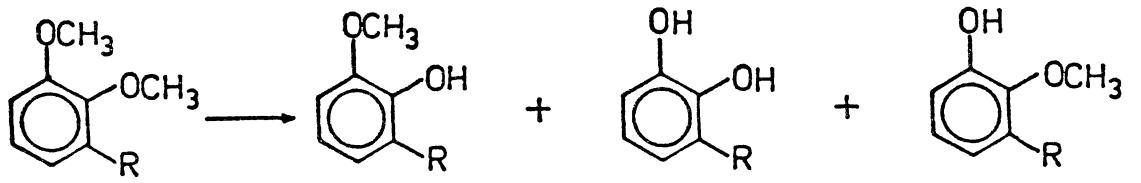
PRODUCT DISTRIBUTION IN THE DEMETHYLATION OF CATECHOL METHYL ETHERS

Starting Material	Equiv. TMSI[a]	Equiv. BBr_3	---Product Ratios[b]---			
			4a	4b	4c	
4a	1.1		21	64	15	
4a		1.1	18	60	22	
4a	3.3		0	0	100	
4a		3.3	0	0	100	
			5a	5b	5c	5d
5a	1.1		6	94	0	0
5a		1.1	40	42	18	0
5a	3.3		0	30	70	0
5a		3.3	0	0	100	0
			6a	6b	6c	6d
6a	1.1		0	96	4	0
6a		1.1	30	24	46	0
6a	3.3		0	47	53	0
6a		3.3	0	0	100	0

[a]Iodotrimethylsilane. [b]Determined through use of LC.

1,2-dimethoxybenzene (4a) with 1.1 equivalents of iodotrimethylsilane or boron tribromide yielded an approximately statistical ratio of 4a, 2-methoxyphenol (4b), and pyrocatechol (4c). Treatment with an excess (3.3 equivalents) of either reagent resulted in quantitative yields of 4c.

Treatment of either the 3-methyl or 3-isopropyl substituted 1,2-dimethoxybenzene (5a and 6a, respectively) with 1.1 equivalents of iodotrimethylsilane yielded a near quantitative amount of the monophenol corresponding to demethylation of the methoxy group flanked by two ortho substituents, 5b or 6b. Reaction of 5a or 6a with 1.1 equivalents of boron tribromide or 3.3 equivalents of iodotrimethylsilane gave a mixture of the catechol, 5c or 6c, and monophenol, 5b or 6b. At no time did the phenol resulting from cleavage of the least hindered methoxy group, either 5d or 6d, form.



5a, R = CH_3 5b, R = CH_3 5c, R = CH_3 5d, R = CH_3
6a, R = i-C_3H_7 6b, R = i-C_3H_7 6c, R = i-C_3H_7 6d, R = i-C_3H_7

The reason for the preferential cleavage of the carbon-oxygen bond of the most crowded methoxy group at C-2 was not intuitively obvious and has only recently been

explained.[4,5] The selectivity of the O-demethylation has been rationalized on the basis of the difference in the proposed conformational orientations of the individual methoxy groups,[4,5] as shown in Figure 1 for 3-methyl-1,2-dimethoxybenzene (5a).

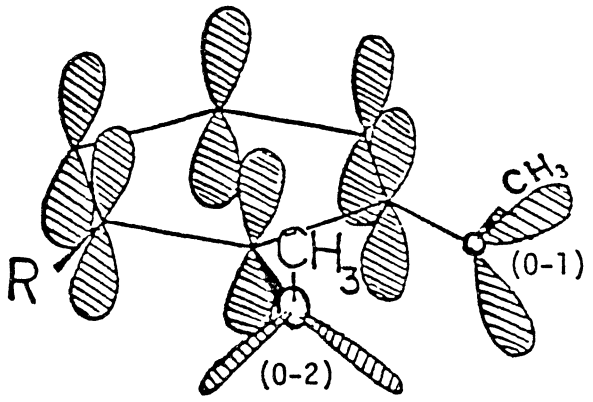


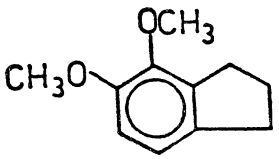
Figure 1. Proposed Conformation of 5a

Presumably steric factors force the methoxy group at C-2 with two ortho neighbors to rotate out of the plane of the aromatic ring, in direct contrast to the methoxy group at C-1 which is coplanar with the ring.[4,5] This suggests an explanation for the regiospecific cleavage of the methoxy at C-2. Given the existence of such a conformer, the electron density of O-2, compared to that of O-1, would be greater since the release of electrons from the methoxy group to the benzene ring is somewhat diminished by the rotation of the lone pair orbitals of the oxygen atom (O-2) out of

conjugation with the pi-orbitals of the ring. Hence, Lewis acids, as electrophilic reagents, would be and are selectively attracted to O-2. The sterically crowded methoxy group may also be more accessible, surprisingly, to attack from a steric standpoint since its lone pair orbitals protrude above and away from the ring, whereas those of the nearby planar methoxy group (O-1) are partially shielded by the adjacent methoxy group.

This concept was built upon data accumulated in this laboratory[4,5] from PRDDO[6] molecular orbital calculations, ^{13}C NMR chemical shifts, and ^{13}C NMR T_1 relaxation measurements. Earlier studies on other systems also indicated such a conformational model.[7,8] Additional information concerning the conformation(s) of such sterically crowded aromatic methoxy groups has since been gained from ^{17}O-NMR studies and single crystal X-ray diffraction analyses, the results of which are presented herein.

In a continuation of the study on the regiochemistry of sterically crowded vicinal aromatic methoxy groups, coupled with a need to develop a selective reductive demethoxylation of compounds typified by 4,5-dimethoxyindan (7) to the



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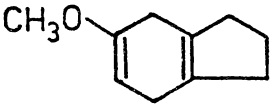

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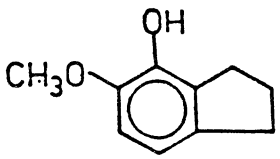

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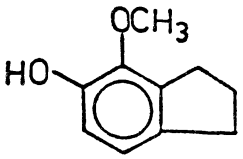


10

diene 8, with a minimum of demethylation to 9 and/or 10, the dissolving metal reactions of various 3-substituted-1,2-dimethoxybenzenes were investigated. The results of these studies constitute a substantial portion of this work.

The use of alkali and alkaline earth metals in refluxing liquid ammonia for the reduction of aromatic compounds dates back to 1937 when Wooster[9] showed that the presence of an alcohol in the reaction medium allowed the reduction of benzene to occur, giving 1,4-dihydrobenzene, whereas in its absence there was no reduction. Wooster[9] also provided evidence that alkyl- and methoxybenzenes are similarly reducible, and described the first reduction of the phenolic ether, anisole, to the corresponding dihydro derivative by the action of sodium and alcohol in liquid ammonia. The reaction found little synthetic application until some years later when A. J. Birch[10] reexamined the method, clarified it, improved it, and utilized it in the reduction of a wide variety of organic compounds. Subsequently, a series of articles appeared on the "reduction by dissolving metals."[10]

Although the dissolving metal reduction of aromatic compounds covers a broad area of chemistry, as borne out by numerous reviews[11-16] on the subject, no systematic work has been done on the reduction of 3-substituted-1,2-dimethoxybenzenes in which steric crowding of the central methoxy group is inherent. There has, however, been an abundance of

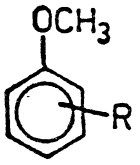
studies on the dissolving metal reductions of aromatic ethers, particularly aryl methyl ethers.

As early as 1886, Freudenberg, Lautsch, and Piazolo[17] discovered that potassium in liquid ammonia acted on methoxybenzene derivatives merely as a demethylating agent. This was also found to be true for sodium, no appreciable reduction occurring.

Birch[10d] subsequently investigated the relative ease of cleavage of various aryl methyl ethers by comparing the amount of phenol obtained upon treatment of the ether with sodium and ammonia. Some of these results are presented in Table II. The effect of substituents on the ease of cleavage

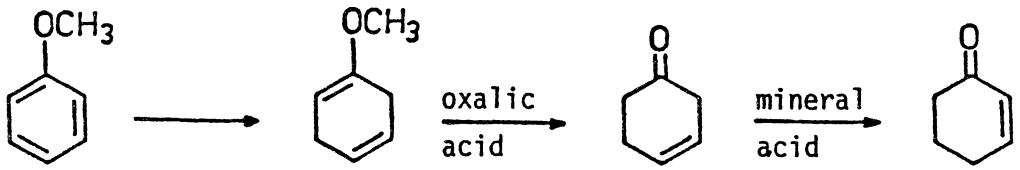
TABLE II

SODIUM/AMMONIA DEMETHYLATION OF ARYL METHYL ETHERS

	% Yield Monophenol
R=H	27
o-Me	17
m-Me	9
p-Me	4
o-OMe	89
m-OMe	71
p-OMe	2.5

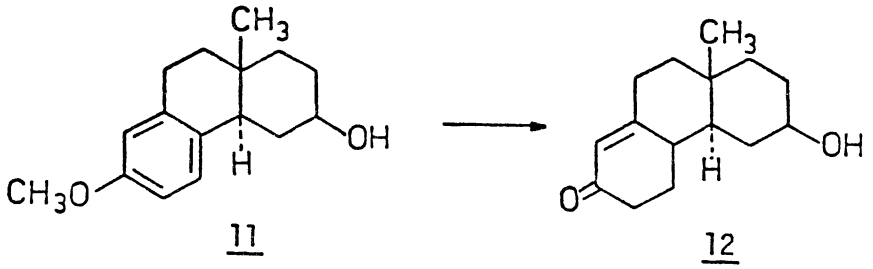
of aryl methyl ethers to the corresponding phenol was thus established as o-methoxy > m-methoxy > hydrogen > o-methyl > m-methyl > p-methyl > p-methoxy. This order is in accord with initial cleavage to phenoxide anion.

Fifty years after Freudenberg's[17] discovery that potassium and ammonia served merely to demethylate methoxybenzenes to phenols, Wooster[9] demonstrated that the addition of a protonating agent, such as methyl alcohol, to the reaction mixture resulted, not in cleavage, but reduction to the 1,4-dihydro derivative. A similar observation was later made by Birch[10a,c] who noted that reduction of anisole with sodium and ethanol in liquid ammonia gave the 2,4-dihydro product which could subsequently be converted by mild acid hydrolysis to the beta,gamma-unsaturated ketone, or by vigorous acid hydrolysis, to the alpha,beta-unsaturated ketone. The reaction sequence can accordingly be written as follows:

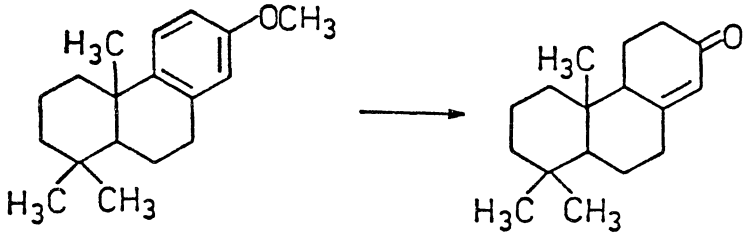


Similar reaction sequences involving more complex systems of this type have provided essential steps in the study of and synthesis of steroids, terpenes, and alkaloids. For example, the anisole derivative 11 gave the ketone 12 which formed the basis of rings B, C, and D in a total synthesis of 11-oxygenated steroids;[18] 13 gave the

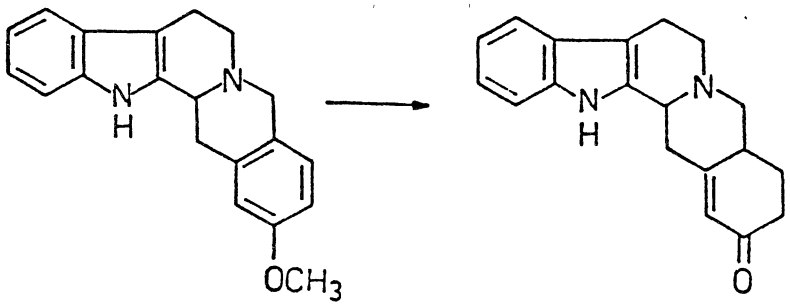
unsaturated ketone 14 used to complete the total synthesis of (+) totarol,[19] and 15 gave 16 which was subsequently converted into yohimbone.[20]



11 12

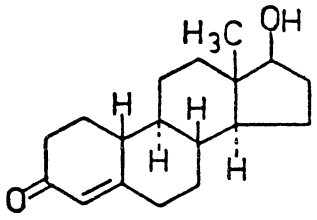


13 14



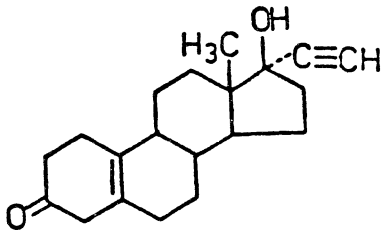
15 16

The utility of this sequence in the synthesis of 19-nor-analogs of steroidal hormones, such as 19-nortestosterone (17),[21-23] has also been well demonstrated.



17

Various 19-norsteroids have been found to have useful clinical activity. For example, ethynodrel (18)[24] was the



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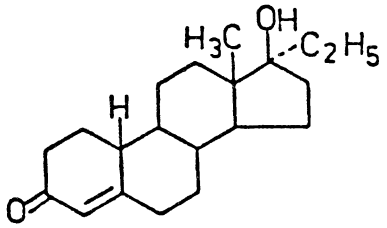
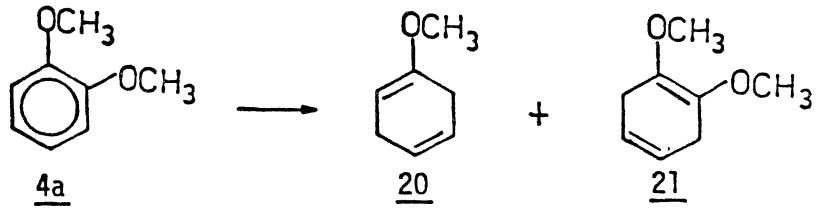


19

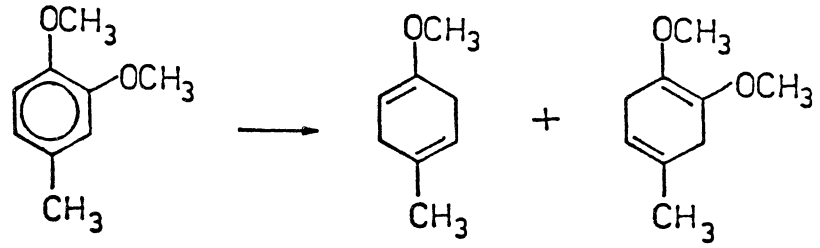
major progestational component of the first commercially offered oral contraceptive.[25] Others, such as norethandrolone (19),[26] are used as oral anabolic agents. These compounds were prepared on an industrial scale for a number of years by the Birch[27] reduction of estradiol derivatives.

Another mode of fission frequently observed in the dissolving metal reductions of aromatic ethers is the loss of alkoxide anion (deoxygenation).[10d,14,16] This occurrence is particularly prevalent with o-dimethoxybenzenes. For example, 4a gives predominantly 2,5-dihydroanisole (20) upon treatment with sodium, ammonia, and alcohol.[10d] Similarly, 4-methyl-1,2-dimethoxybenzene (22) is converted primarily to

2,5-dihydro-4-methyl-anisole (23). Some of the dimethoxy derivative 24 is also formed.[10d]



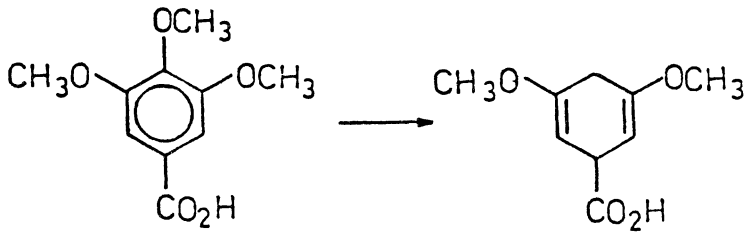
4a 20 21



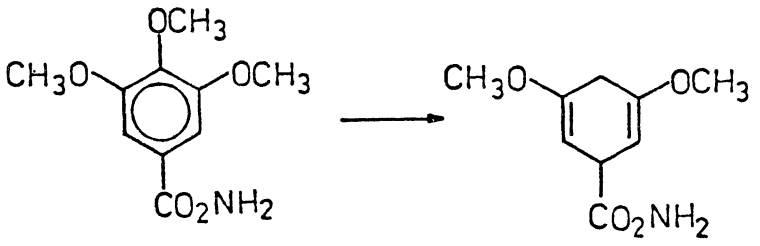
22 23 24

Methoxy groups situated para to a carboxy or amide group, and to a lesser extent ortho, are also very susceptible to removal from the aromatic nucleus due to the electronic nature of the carboxyl group. Here it may be noted the conversion by sodium and ethanol in liquid ammonia of 3,4,5-trimethoxybenzoic acid (25) to 1,4-dihydro-3,5-dimethoxybenzoic acid (26),[28] of 3,4,5-trimethoxybenzamide (27) to 1,4-dihydro-3,5-dimethoxybenzamide (28),[29] and 3,4-dimethoxybenzoic acid (29) to 3-methoxycyclohex-2-ene carboxylic acid (30).[28]

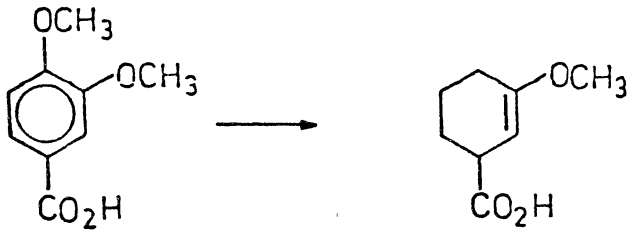
Methylenedioxybenzenes also undergo a facile reduction of oxygen from the ring. The cleavage of these substances was first investigated by Freudenberg and colleagues.[17,30]



25 26

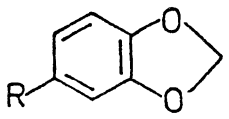


27 28



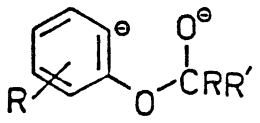
29 30

They discovered that potassium in liquid ammonia converted dihydrosafrole (31a; R=n-C_3H_7) to p-hydroxyphenylpropane, and piperonylic acid (31b;R=CO_2H) to m-hydroxybenzoic acid. Subsequently, Birch[10d] converted methylenedioxybenzene (31c; R=H), 3,4-methylenedioxytoluene (31d; R=CH_3), and safrole (31e; R=$CH_2CH=CH_2$) with sodium and alcohol in ammonia to phenol, p-cresol, and p-allylphenol, respectively. The

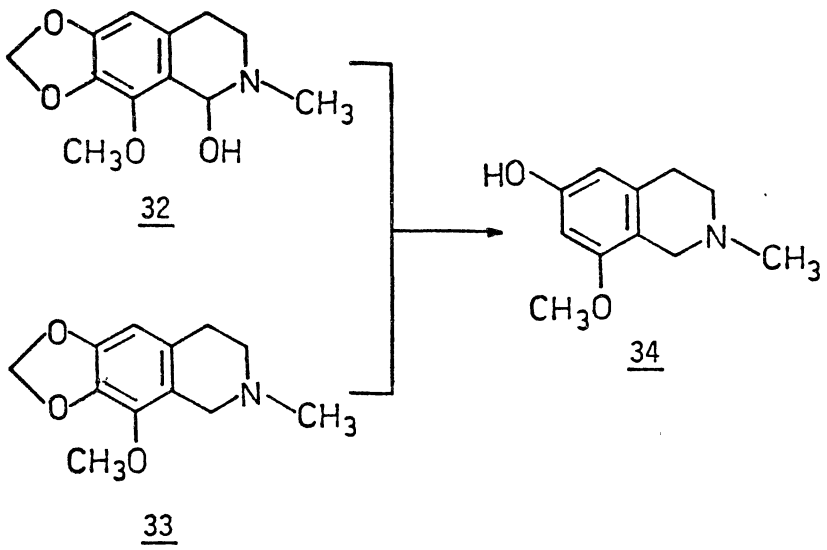


31

same products were obtained in the absence of an alcohol. Birch[10d] has explained these results as initial cleavage to a dianion such as that shown below in which a negative charge on the aromatic ring is produced para to the group more capable of stabilizing it (CO_2H > H > CH_3). The



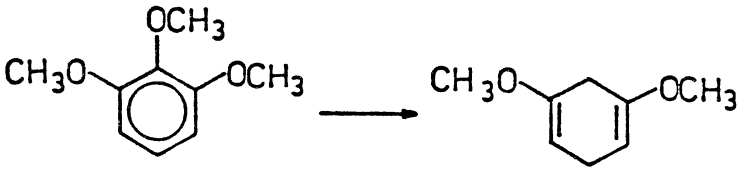
catechol acetal groupings in cotarnine (32) and the isoquinoline 33 are cleaved during the reduction with sodium and ammonium chloride in ammonia to the phenol 34.[31] The benzylic hydroxyl group in 32 is also cleaved in the process.



The deoxygenation of aromatic ethers and catechol acetals appears to be controlled by the substitution on the aromatic nucleus. In all of the reactions noted above, the fissions can be correctly predicted on the basis of earlier

studies on the effect of substituents on the cleavage of aryl methyl ethers[10d] and diphenyl ethers.[32]

As previously stated, there exists very little information on the dissolving metal reduction of compounds containing both a sterically hindered methoxy group, one flanked by two neighbors, and a less hindered one. It was of interest, therefore, to determine whether such compounds, under similar conditions, would be susceptible to dealkylation, deoxygenation, and/or nuclear reduction, occurrences which are often observed with aromatic ethers as described in the preceeding pages. More importantly, would there be preferential reaction of the crowded methoxy group as was exhibited in the Lewis acid demethylations[2] of such compounds. One isolated example, the sodium/ammonia-ethanol reduction of 1,2,3-trimethoxybenzene (35) to yield the deoxygenated, dihydro product 36[10d] does suggest that such selectivity in cleavage is possible.



35 36

CHAPTER II

RESULTS AND DISCUSSION

^{17}O-NMR Studies

As previously written, the specific cleavage of the carbon-oxygen bond of the most crowded methoxy group at C-2 in 3-alkyl-1,2-dimethoxybenzenes[2] has been explained on the basis of the difference in the conformations of the respective methoxy groups[4,5] as shown in Figure 1 for 5a. The rotation of the lone pair orbitals of the sterically hindered methoxy group out of conjugation with the pi-orbitals of the aromatic ring suggests a decrease in the electron-donating ability of this oxygen atom to the ring compared to that of the other planar methoxy group. It is to be expected, therefore, that the electron densities of these two methoxy oxygen atoms would differ.

Such expectations were reinforced by molecular orbital calculations carried out on various methoxybenzenes which predict that the electron density on the methoxy oxygen will increase as the methoxy group is rotated out of the plane of the aromatic ring.[4,5] Similar calculations for the methoxy carbon predict the opposite effect. Theoretically, the electron density on the methoxy carbon should decrease as a result of the loss of double bond character of the aromatic

carbon-oxygen bond, thus deshielding the carbon. This is indeed what is observed.[4,5]

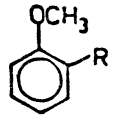
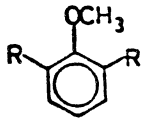
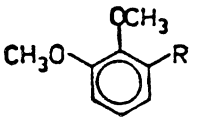
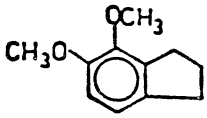
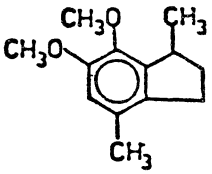
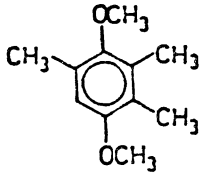
Interest in probing the electronic environments of a sterically crowded methoxy group which is thought to lie perpendicular, or near perpendicular, to the aromatic ring on which it is situated and a methoxy group with a planar arrangement, prompted an investigation into the ^{17}O-NMR spectra of various methoxybenzenes. In a very qualitative manner, ^{17}O chemical shifts can be taken as a probe of electronic density modification in a homologous series of compounds.

^{17}O-NMR spectroscopy has found limited application due to the experimental problems associated with a quadrupolar nucleus having low natural abundance (0.037%).[33] Due to advances in Fourier transform NMR instrumentation, however, it has been possible to observe this nucleus[34-44] in unenriched compounds, among them ethers,[34] substituted anisoles,[35] acetophenones and benzaldehydes,[40] oxiranes,[43] and hydroxycyclohexanes,[44].

Fourier transform ^{17}O-NMR spectra were measured for a number of substituted monomethoxy- and dimethoxybenzenes in natural abundance at 40.66 MHz. It is apparent from the observed data collected in Table III that the methoxy oxygen chemical shifts are dependent upon the number of neighbors flanking, that is, ortho to, the methoxy substituent. There is an obvious upfield chemical shift for the oxygen of a methoxy group flanked by two ortho substituents. In the case

TABLE III

^{17}O-NMR CHEMICAL SHIFTS OF METHOXY OXYGENS

Methoxybenzene			^{17}O Chemical Shift[a]	
			O-1[b]	O-2[c]
	37	R = H	48.0	
	38	Me	46.2	
	39	t-Bu	48.8	
	4a	OMe	33.5	
	40	R = Me		16.5
	41	i-Pr		13.5
	42	t-Bu		27.3
	5a	R = Me	36.4	10.5
	43	Et	35.8	9.4
	6a	i-Pr	36.1	8.7
	35	OMe	37.1	-6.1
	7		27.2	12.6
	44		26.8	7.6
	45		40.7	9.8

[a]Relative to tap water (ppm). [b]Refers to outside, unhindered methoxy. [c]Refers to methoxy with two ortho substituents.

of the 3-substituted-1,2-dimethoxybenzenes and indan systems, there are significant differences in the two individual methoxy shifts, the oxygens of the less hindered methoxy groups giving rise to the more downfield shifts. To illustrate the uniqueness of ^{17}O-NMR spectra, several representative spectra are presented in Appendix B (Spectra 1-6).

X-ray Diffraction Analyses

As evidenced by the differences in the ^{17}O-NMR chemical shifts, the electronic environments of a methoxy group with two ortho neighbors and one with none or only one differ. It is reasonable to assume that this difference stems from a fundamental difference in the conformational orientations of such methoxy groups in which one of the conformations restricts electron donation to the benzene ring more so than the other. As stated in Chapter I, an out-of-plane orientation has been suggested.[4,5]

X-ray crystal structure determinations of 1,2,3-trimethoxy systems[45-49] show that the center methoxy groups are not coplanar with the aromatic ring. Single crystal X-ray diffraction studies performed by Dr. E. M. Holt on a similar system, 3-(2,3-dimethoxyphenyl)propanoic acid (46), also revealed an out-of-plane orientation for the sterically crowded methoxy group.

Figure 2 is a projection of the asymmetric unit of 46, henceforth referred to as structure I. The two molecules of

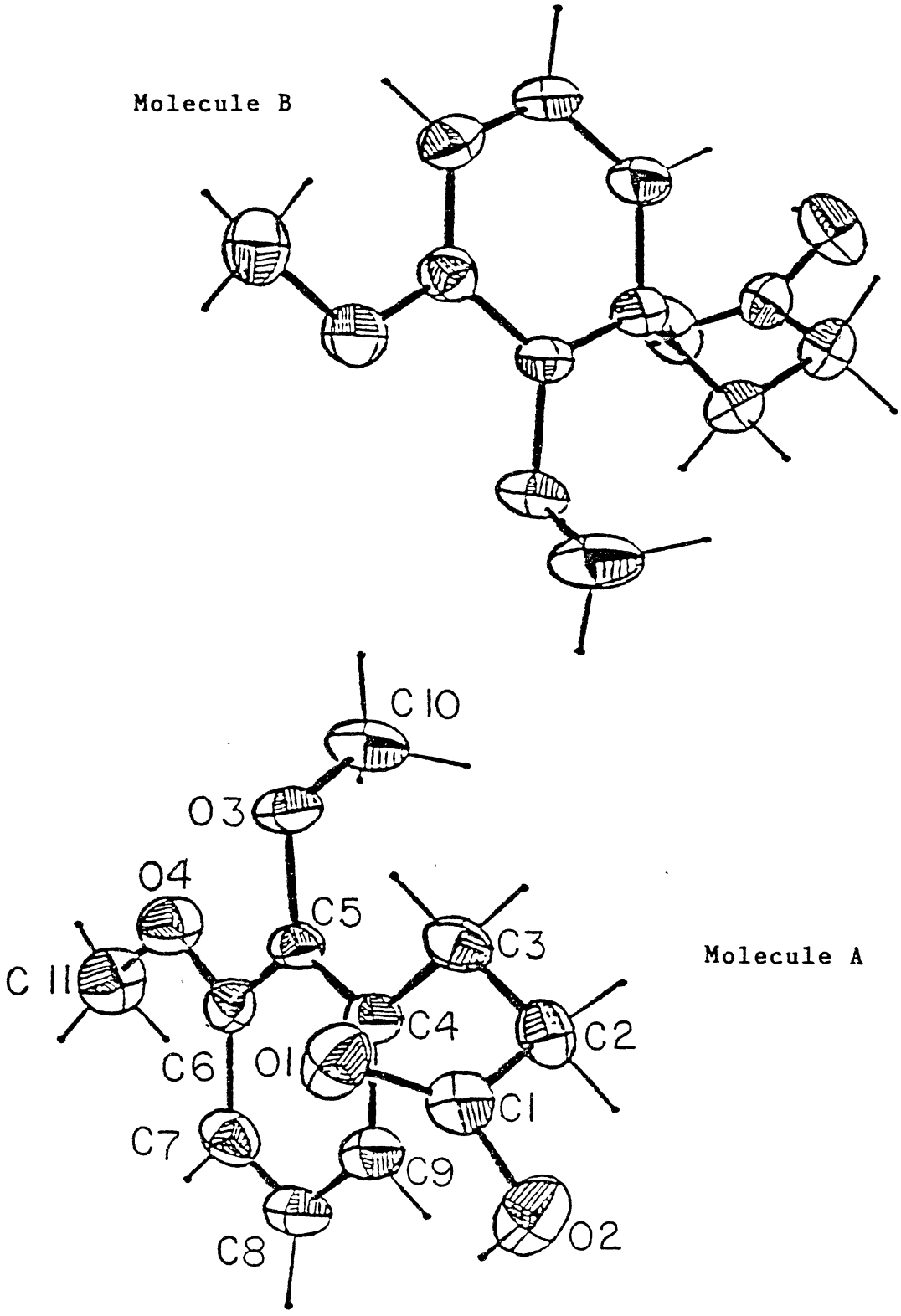


Figure 2. Projection of the Asymmetric Unit of 46

the unit are structurally similar and exhibit normal bond angles and distances (Table IV). In both molecules A and B, the terminal methoxy group containing atom O(4) faces away from the other ring substituents and is nearly coplanar with the plane of the aromatic ring (0.106Å difference between the O(4), C(11), C(6) plane and the plane of the ring in molecule A; 0.108Å difference in molecule B). Steric effects, however, prevent both methoxy groups of the molecule, either A or B, from being in or near the plane of the aromatic ring. The carbon atom of the middle methoxy is thus rotated near perpendicular to the plane of the ring (80.47° in molecule A; 81.55° in molecule B) and leans towards the neighboring $CH_2CH_2CO_2H$ substituent and away from the adjacent methoxy group.

Projections of the crystalline material resulting from treatment of a solution of 46 with *d*-2-amino-1-phenylpropane (47a) (structure II) and separately with the *ℓ*-isomer 47b (structure III) are shown in Figure 3. The crystal data for these structures, presented in Table V, are very similar. The angle between the plane formed by atoms O(3), C(5), C(10) and the plane of the benzene ring is 67.5° in II and 66.7° in III with the center methoxy group in each crystal assuming an arrangement opposite to that observed in I in which it leans towards the $CH_2CH_2CO_2H$ substituent and away from the ortho methoxy. The unit cell of II selectively contains the S modification of the acid with respect to the

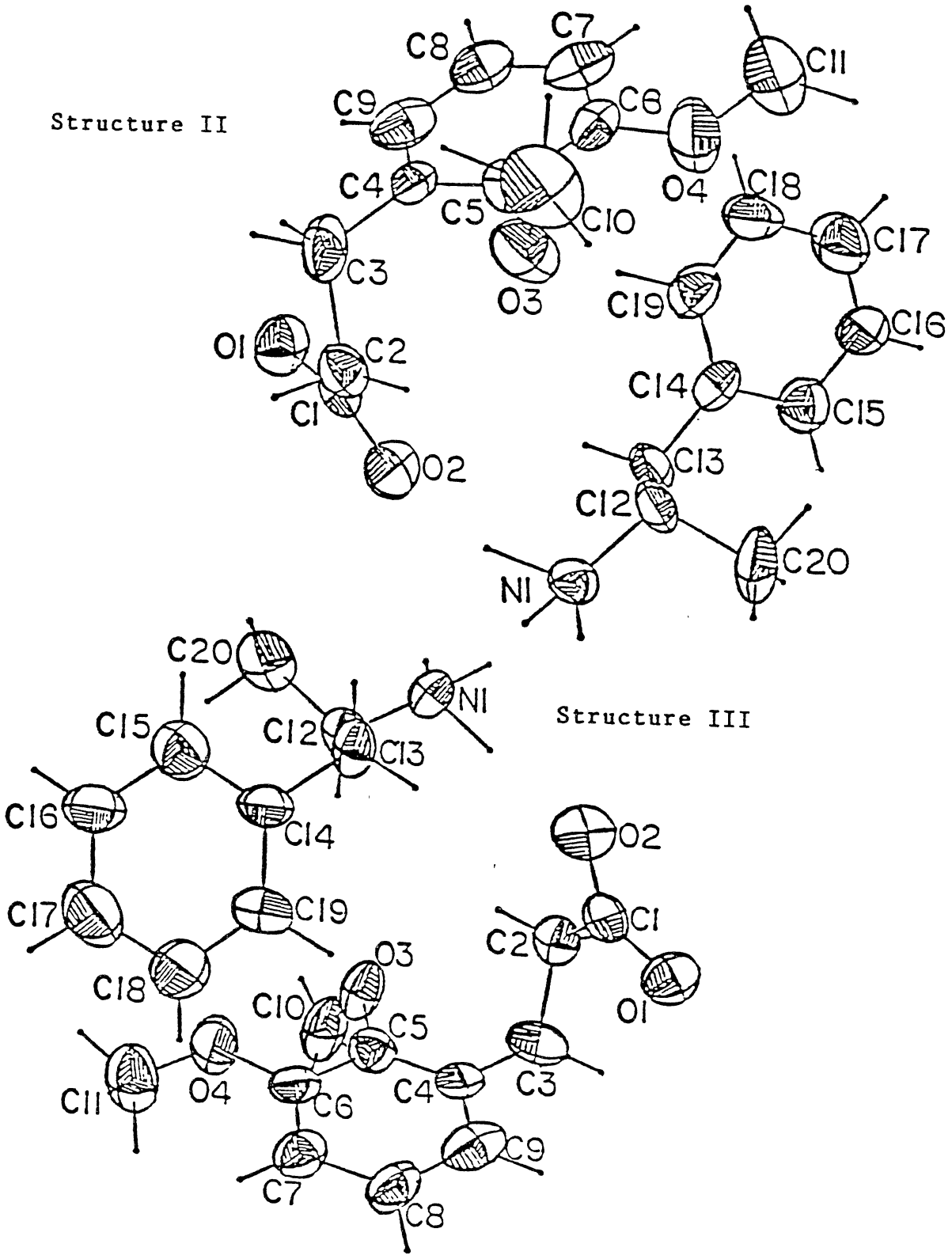


Figure 3. Crystal Structures of the *d*-Amine Salt of 46 (II) and the *ℓ*-Amine Salt of 46 (III)

TABLE IV

BOND ANGLES (°) AND BOND LENGTHS (Å) FOR 46 AND THE AMINE SALTS OF 46 (II AND III)

	I		II	III
	Molecule A	Molecule B	*d* isomer	*l* isomer
C1 - O1	1.220(4)	1.220(5)	1.236(10)	1.222(14)
C1 - O2	1.303(4)	1.304(5)	1.271(11)	1.276(15)
C1 - C2	1.507(5)	1.509(4)	1.490(13)	1.522(17)
C2 - C3	1.519(4)	1.519(5)	1.542(13)	1.533(16)
C3 - C4	1.511(6)	1.517(5)	1.511(13)	1.508(16)
C4 - C5	1.397(4)	1.391(5)	1.371(13)	1.385(17)
C4 - C9	1.392(5)	1.397(4)	1.382(13)	1.385(18)
C5 - C6	1.389(5)	1.404(5)	1.386(12)	1.368(15)
C5 - O3	1.393(5)	1.391(5)	1.384(11)	1.403(14)
C6 - C7	1.394(6)	1.392(6)	1.375(14)	1.374(19)
C6 - O4	1.371(4)	1.365(5)	1.375(12)	1.399(16)
C7 - C8	1.379(5)	1.376(6)	1.367(15)	1.381(19)
C8 - C9	1.381(6)	1.391(6)	1.384(16)	1.378(21)
O3 - C10	1.433(5)	1.437(5)	1.450(11)	1.454(17)
O4 - C11	1.429(6)	1.440(6)	1.367(12)	1.361(15)
C12 - C13			1.537(13)	1.556(16)
C12 - C20			1.493(14)	1.497(19)
C12 - N1			1.468(10)	1.457(13)
C13 - C14			1.522(12)	1.519(16)
C14 - C15			1.380(13)	1.396(16)
C14 - C19			1.369(13)	1.364(17)
C15 - C16			1.390(14)	1.405(18)
C16 - C17			1.345(17)	1.323(22)
C17 - C18			1.352(16)	1.381(21)
C18 - C19			1.380(15)	1.385(20)

TABLE IV (Continued)

	I		II	III
	Molecule A	Molecule B	*d* isomer	*ℓ* isomer
O1 - C1 - O2	123.6(3)	123.8(3)	122.1(8)	124.4(11)
O1 - C1 - C2	123.6(3)	123.6(3)	120.7(8)	119.9(11)
O2 - C1 - C2	112.7(3)	112.6(3)	117.0(6)	115.6(10)
C1 - C2 - C3	114.2(3)	114.2(3)	115.2(8)	113.9(10)
C2 - C3 - C4	115.5(3)	115.3(3)	114.3(7)	115.7(9)
C3 - C4 - C5	118.6(3)	118.4(3)	119.2(8)	120.2(11)
C3 - C4 - C9	123.8(3)	123.4(3)	122.7(8)	122.0(11)
C5 - C4 - C9	117.6(3)	118.2(3)	118.1(9)	117.8(11)
C4 - C5 - C6	121.7(3)	121.6(3)	120.7(9)	121.2(11)
C4 - C5 - O1	118.3(3)	118.9(3)	118.5(8)	117.4(10)
C6 - C5 - O3	119.8(3)	119.3(3)	120.7(8)	121.3(10)
C5 - C6 - C7	119.5(3)	118.9(3)	120.8(9)	121.2(12)
C5 - C6 - O4	124.6(3)	125.1(3)	124.3(8)	123.7(10)
C6 - C7 - C8	119.1(4)	119.8(3)	118.6(9)	117.9(12)
C7 - C8 - C9	121.2(4)	121.2(4)	120.7(9)	121.3(12)
C8 - C9 - C4	120.8(3)	120.2(3)	120.9(9)	120.4(12)
C5 - O3 - C10	115.0(3)	114.2(3)	113.5(7)	113.2(9)
C6 - O4 - C11	117.1(3)	116.7(3)	120.3(8)	120.6(10)
C7 - C6 - O4	124.6(3)	125.1(3)	124.3(8)	123.7(10)
C13 - C12 - C20			113.5(7)	113.2(9)
C13 - C12 - N1			107.4(7)	108.3(9)
C20 - C12 - N1			109.4(7)	110.0(10)
C12 - C13 - C14			111.8(7)	112.7(8)
C13 - C14 - C15			119.5(8)	119.0(10)
C13 - C14 - C19			121.8(8)	122.4(10)
C15 - C14 - C19			118.7(8)	118.7(10)
C14 - C15 - C16			118.4(9)	117.3(11)
C15 - C16 - C17			122.4(10)	123.6(13)
C16 - C17 - C18			119.1(10)	119.3(13)
C17 - C18 - C19			120.2(10)	118.8(14)
C18 - C19 - C14			121.1(9)	122.4(12)

TABLE V

CRYSTAL DATA FOR 46 AND THE AMINE SALTS OF 46 (II AND III)

	(I)	(II)	(III)
Formula	$C_{11}H_{14}O_4$	$C_{20}H_{27}N_1O_4$	$C_{20}H_{27}N_1O_4$
MWT	210.24	345.48	345.48
a	5.083(1)Å	16.738(8)Å	16.770(9)Å
b	15.351(3)	17.255(16)	17.320(6)
c	14.149(5)	6.663(5)	6.720(6)
α	103.14(2)	90°	90°
β	100.36(2)	90	90
γ	90.02(2)	90	90
V	1056.59(47)Å^3	1924.3(26)Å^3	1952.0(26)Å^3
F(000)	448	744	744
μMoK_α	1.180	0.965	0.951
λMoK_α	0.71069Å	0.71069Å	0.71069Å
D_{calc}	1.32 g cm^{-1}	1.192 g cm^{-1}	1.175 g cm^{-1}
Z	4	4	4
Obs. refl.	3734	1061	1031
R	6.4%	6.3%	7.5%
Space group	$P\bar{1}$	$P2_12_12_1$	$P2_12_12_1$

stereochemistry at C(5); that of III contains the R enantiomer.

Bond distances and angles for II and III are presented in Table IV. All the values are quite normal except for the length of the methyl-oxygen bond of the planar methoxy group (O(4)-C(11)) and the bond angle of this methoxy (C(6)-O(4)-C(11)). The O(4)-C(11) distances in II and III are significantly shorter, 1.361Å and 1.367Å respectively, compared to normal distances of 1.429-1.454Å. This decrease in the O(4)-C(11) bond length implies that O(4) has assumed greater sp^2 character than has O(3). The angles at these same oxygens are larger, 120.3(8)° and 120.6(10)° respectively, compared to 113-117° for other methoxy groups. The close proximity of the terminal methoxy group and the ortho hydrogen atom is perhaps responsible for this increase.

The X-ray diffraction analyses of I, II, and III confirms that an aromatic methoxy group flanked by two ortho neighbors may assume either an R or S configuration presumably due to a barrier of rotation about the aromatic carbon-oxygen bond. As such, these stereoisomers may be selectively crystallized with a chiral resolving agent.

Such a phenomena can be described by the term "atrop-isomerism,"[50] which denotes any kind of stereoisomerism caused by restricted rotation about single bonds in which the isomers can actually be isolated. Early examples of molecules exhibiting such behavior were all biphenyl

derivatives.[50] At this time, a new term "dysanatopic" [dys(uncomfortable)ana(upward)topic(place)] is also suggested to describe crowded functional groups such as the methoxy group at C-2 of 46. This term, however, is reserved for use in describing those groups that display significant regiochemistry, an enhanced rate of reaction, or a spectroscopic deviation from normal.

Dissolving Metal Reductions

The study of the dissolving metal reductions of 3-substituted-1,2-dimethoxybenzenes initially focused on the reduction of 3-methyl-1,2-dimethoxybenzene (5a). The reduction was carried out under conditions similar to those described by Birch[10c] for the reduction of methoxyalkylbenzenes whereby an excess of the alkali metal, usually sodium, was added to a vigorously stirred, homogeneous solution of the aromatic ether, liquid ammonia, and alcoholic proton source. For the purposes of this present study, however, lithium was substituted for sodium.[51] tert-Butyl alcohol was originally chosen as the proton source for the reduction of 5a. Upon completion of the addition of the metal, the mixture was stirred at reflux (-33 ^{o}C) until the blue color characteristic of metal-ammonia solutions had disappeared. The alkaline reaction mixture was then extracted with ether and the remaining aqueous layer was acidified with dilute hydrochloric acid and subsequently extracted with ether, thereby resulting in

separation of the mixture into base-insoluble (neutral) and base-soluble (phenolic) materials.

The outcome of the lithium/ammonia-tert-butyl alcohol reduction of 5a is shown in Figure 4. The major component (90% by gas chromatography) of the base-insoluble fraction was identified by proton NMR, carbon NMR, and mass spectrometry as 1-methoxy-5-methylcyclohexa-1,4-diene (48)

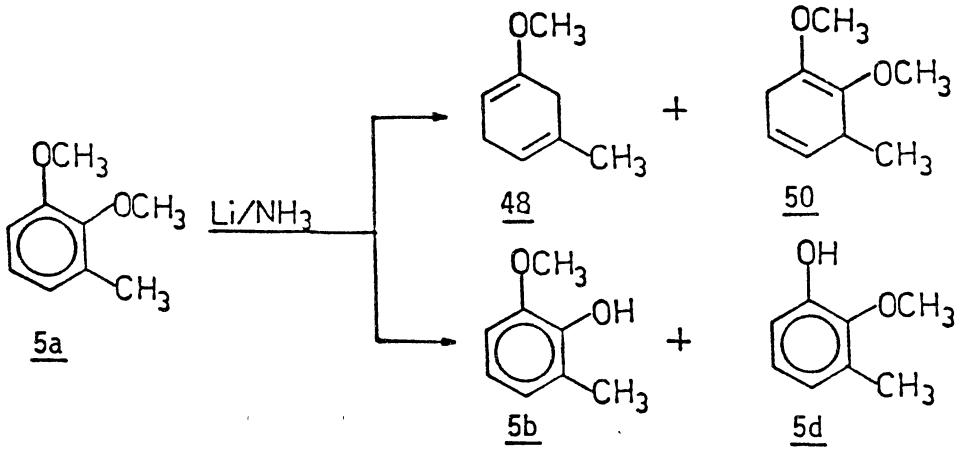


Figure 4. Reaction Products from the Lithium/Ammonia-tert-Butyl Alcohol Reduction of 5a

in an overall yield of 44%. Formation of 48 involved not only reduction of the aromatic nucleus to the dihydro derivative but also loss of the crowded methoxy group (deoxygenation) at C-2. The identity of this product was confirmed by mineral acid hydrolysis to the alpha,beta-unsaturated ketone, 3-methyl-cyclohex-2-enone (49). In

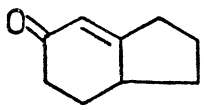
addition to trace amounts of what are believed to be more highly reduced products, the dihydro product 50 was also identified as a component of the neutral fraction in an overall yield of approximately 2%. It is conceivable that the dihydro derivative in which the least sterically crowded methoxy group was expelled from the ring was present as one of the minor components of the neutral mixture. Physical evidence, however, failed to establish its presence or absence. It is because of this uncertainty that the deoxygenation is described, not as specific, but as selective.

Gas chromatographic analysis of the base-soluble fraction revealed the presence of two components in a ratio of 95:5. These were determined to be the two possible phenols 5b and 5d derived from demethylation of the individual methoxy groups of the starting material. The major isomer was established to be the phenol resulting from cleavage of the oxygen-carbon bond of the more sterically hindered methoxy group, a result consistent with that obtained previously in the Lewis acid demethylation studies.[2] No catechol product was noted.

The reduction of 5a was repeated using absolute ethanol as the proton source. Aside from a shorter reaction time, as evidenced by a more rapid disappearance of the characteristic blue color, the only detectable difference between the reaction employing ethanol and that employing tert-butyl alcohol as proton source was not in the

identities of the products, but in their relative yields. More phenolic material was formed in the reduction using tert-butyl alcohol. Discussion of the significance of this difference in relative yields will be deferred until later in this chapter.

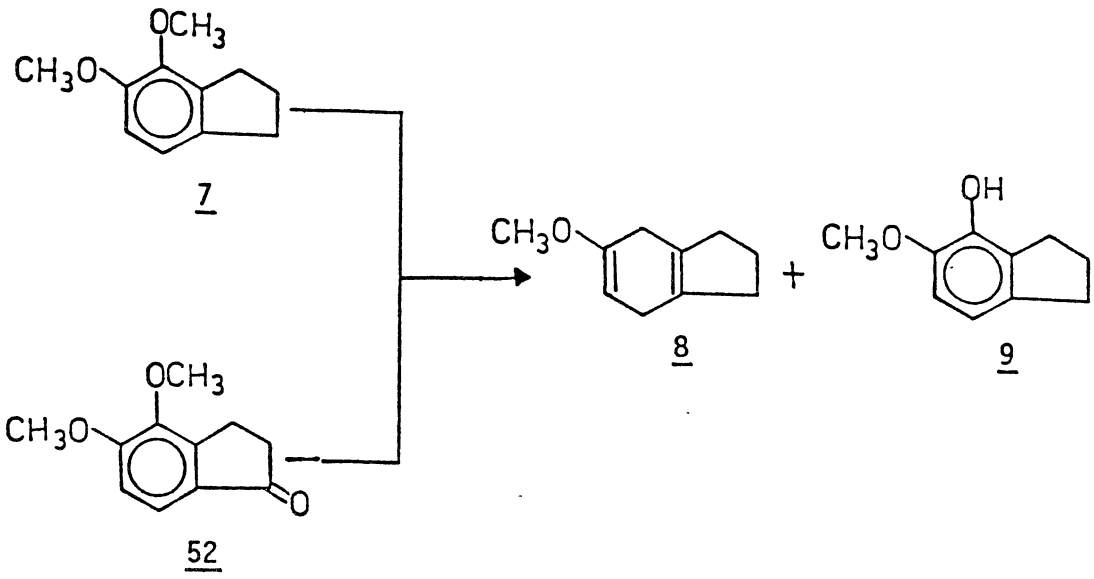
In order to substantiate this preliminary finding that the observed dealkylation and deoxygenation of 3-substituted pyrocatechol ethers is selective under dissolving metal conditions, several other catechol ethers were subjected to reduction under similar conditions. As reported by Birch,[10d] 35 gives 36 upon treatment with sodium, ammonia, and ethanol. Under the conditions employed for this study, that is, lithium, ammonia, and ethanol, 35 was converted to 36 in 92% isolated yield. No phenol was detected. In the lithium/ammonia-ethanol reduction of 4,5-dimethoxyindan (7), 4,7-dihydro-5-methoxyindane (8) was established as the major component (95% by gas chromatographic analysis) of the base-insoluble or neutral material, an overall yield of 79%. The identity of 8 was confirmed by acid hydrolysis to the alpha,beta-unsaturated ketone 51 illustrated below. The



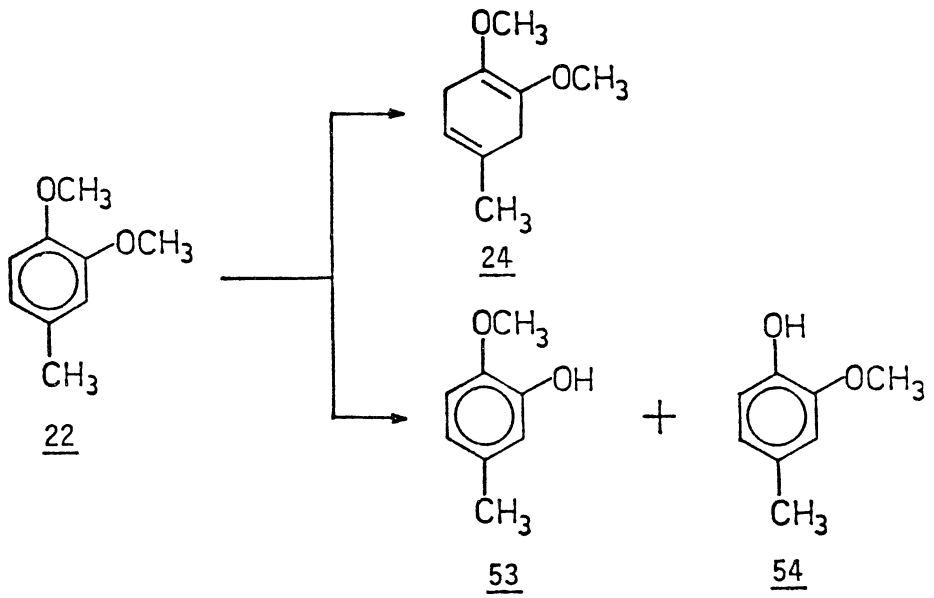
51

base-soluble material from the reaction was shown to be exclusively 4-hydroxy-5-methoxyindan (9), the phenol resulting from dealkylation of the most crowded methoxy at C-4. Similarly, the reduction of the corresponding indanone

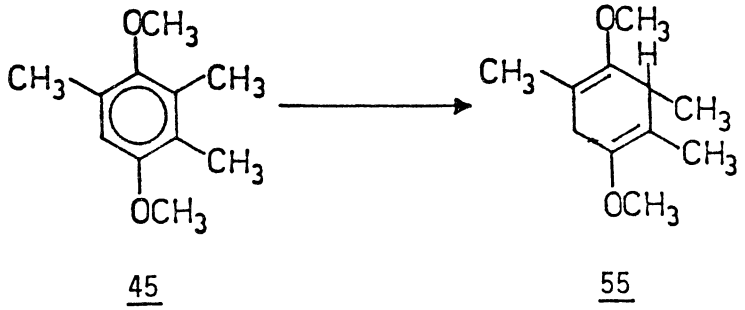
52 gave the same products. However, in the latter case a substantial number of other products were obtained. Distillation (vacuum and/or atmospheric pressure) failed to separate these products, hence, their identities are not known.



In all of the aforementioned reactions, selective dealkylation and/or deoxygenation of the methoxy group flanked by two ortho substituents was observed. Where no such methoxy group exists, as in 4-methyl-1,2-dimethoxybenzene (22), the major component 24 of the base-insoluble material (88% by gas chromatography) retained both methoxy groups. The base-soluble fraction consisted of phenols 53 and 54 in a ratio of 3 to 2, respectively, a ratio considerably less selective than that obtained in the reduction of 5a.



Compound 45, which contains one methoxy group with two ortho neighbors and one less crowded methoxy, was subjected to reduction under standard conditions in order to determine whether there would be selective deoxygenation and/or dealkylation of the methoxy groups as observed in the previously described reductions. Starting material, however, was recovered quantitatively. This lack of reaction



indicated the need for a more effective reducing system. The method described by Wilds and Nelson[33a] was chosen. This method differs from the usual procedure in that the alcohol is not present at the onset of the reaction but is instead

added to a solution of the substrate, ammonia, lithium, and co-solvent (if necessary). Under these conditions, the dihydro product 55 was generated in 78% yield with no detectable deoxygenation or dealkylation of either methoxy group. Although unexpected, this complete lack of cleavage in the dissolving metal reduction of 45 can be rationalized, and indeed will be later in this discussion.

The reduction of yet another 3-substituted pyrocatechol ether, 2,3-dimethoxybenzoic acid (56) with lithium, ammonia, and ethanol gave 3-hydroxybenzoic acid (57) in 86% isolated yield. Admittedly, this ether differs from the others in that there is no alkyl substituent but instead a carboxyl substituent. Similar to the others, however, the methoxy group flanked by two ortho neighbors was selectively expelled from the aromatic nucleus. The remaining methoxy also underwent demethylation to the phenol.

It was written earlier (page 28) that the lithium/ammonia reduction of 5a with either tert-butyl alcohol or ethanol as proton source gave a similar array of products, their relative yields, however, differed. That is, the base-insoluble (neutral) to base-soluble (phenolic) product ratios differed. This suggested that the identity of the proton source has an influence on the demethylation and demethoxylation processes. To determine this influence, several anhydrous alcohols of varying acidity were used as the proton source in the reduction of 5a. These results are summarized in Table VI.

TABLE VI

LITHIUM/AMMONIA REDUCTION OF 5a

ROH	Neutral/Phenolic[a,b]	pK_a[c]	% Yield 48	5b	5d
$(C_2H_5)_3COH$	0.8	d	32	44	5
t-BuOH	2.7	19.0	44	15	1
i-PrOH	7.6	17.1	68	8.5	0.5
EtOH	12.0	15.9	50	3.5	<1
MeOH	19.4	15.1	64	3	<1
CF_3CH_2OH	e	12.4		e	

[a]Based on the weight of each fraction. [b]Starting material essentially consumed in all cases that gave product. [c]See reference 52. [d]Not available. [e]No product - Starting material quantitatively recovered. A blue color was not observed.

An interesting trend was observed as the acidity of the proton source increased from 3-ethyl-3-pentanol to methanol, the neutral/phenolic ratio increased as well. However, in the presence of a stronger acid such as 2,2,2-trifluoroethanol, neither reduction nor cleavage occurred and starting material was recovered quantitatively. In the absence of an added proton source, demethylation to yield phenols became the dominant process accounting for 72% combined yield. Starting material (10%) was also recovered.

It was initially presumed that phenol formation in the presence of an alcohol resulted from the nucleophilic substitution of the methyl of the methoxy group by alkoxide ion. This postulate was based on the knowledge that aromatic ethers undergo nucleophilic substitution of the alkyl group by a variety of reagents, among them potassium hydroxide,[53] Grignard reagents,[54] and mercaptide ions.[55] If nucleophilic substitution was indeed occurring, more phenol formation would be expected in the presence of a better nucleophile. The results of Table VI support this theory. More phenolic material was obtained with tert-butyl alcohol than with methanol - tert-butoxide being the better nucleophile. In order to determine whether nucleophilic substitution of either of the methoxy groups in 5a was possible, a solution of 5a and diethyl ether was refluxed with potassium tert-butoxide. After three hours of refluxing, starting material was quantitatively recovered. Similar reaction in dimethoxy ethane also gave no phenol.

As has been demonstrated, the lithium/ammonia reduction of 3-substituted-1,2-dimethoxybenzenes generates several types of products, among them, dihydro products, dealkylated products, and deoxygenated, dihydro products. A mechanistic scheme rationalizing their formation is presented as Figure 5 for 3-methyl-1,2-dimethoxybenzene (5a). It is suggested that all products proceed via a common intermediate, a radical anion 58. This is in agreement with the generally accepted mechanism of dissolving metal

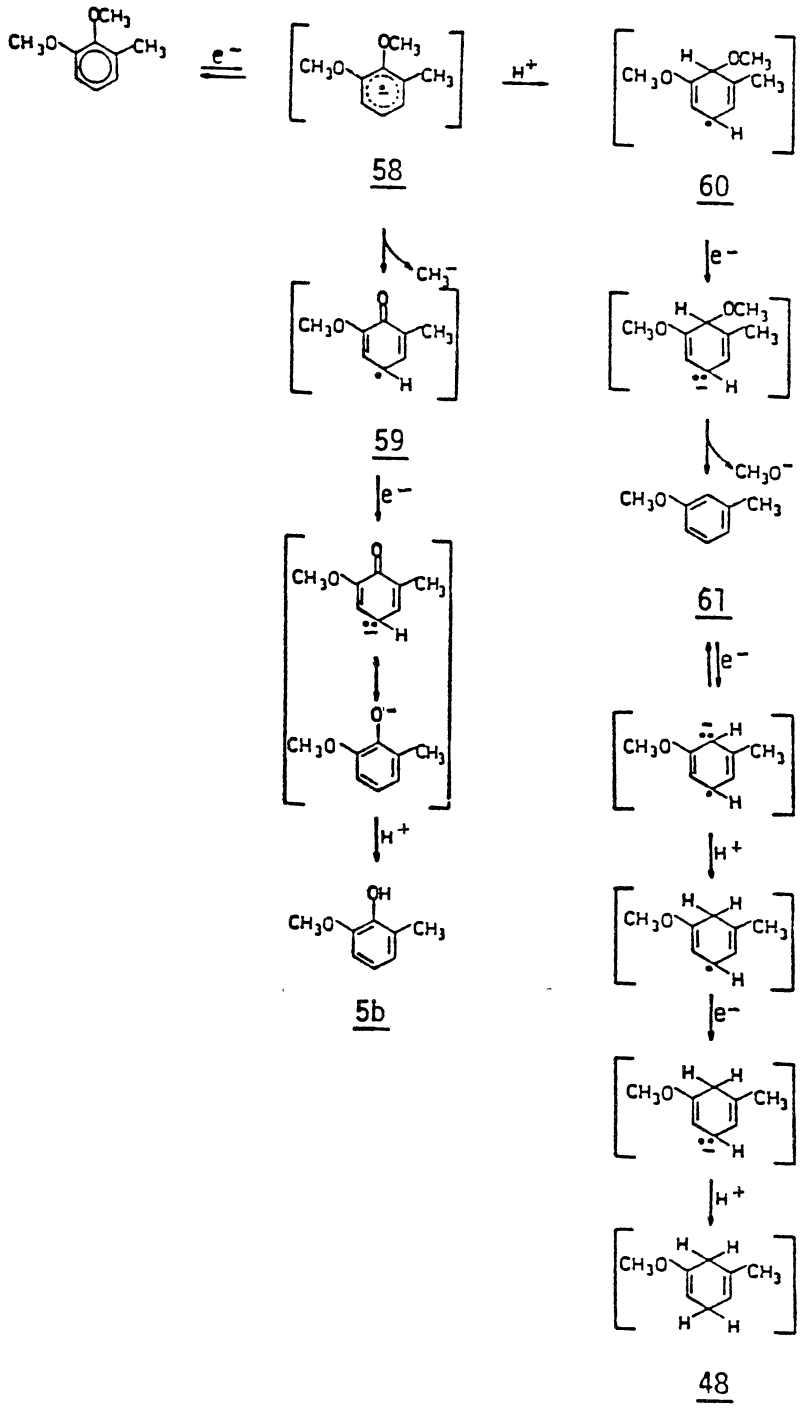


Figure 5. Proposed Mechanism for the Dissolving Metal Reduction of 5a

reductions of monobenzenoid compounds,[13-16,56-60] a topic which has been debated for many years.

The mechanism was first discussed in terms of possible addition of hydrogen atoms,[10a,61,62] however, this theory was abandoned in favor of a mechanism involving the preliminary addition of two electrons to the aromatic nucleus, followed by the addition of two protons[11,51a,63] as shown in Figure 6. The preference for maximum separation of

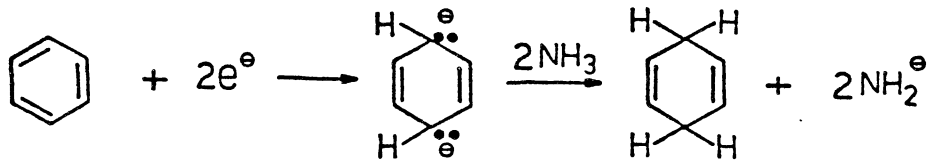


Figure 6. Dianion Mechanism for the Dissolving Metal Reduction of Monobenzenoid Compounds

charge in the dianion provided a reasonable explanation for the formation of 1,4-dihydrocompounds. Unfortunately, this mechanism was incompatible with some of the experimental data since it could not account for the failure of reduction in the absence of an alcohol.[10f] This left the alternative mechanism, a radical anion mechanism, shown in Figure 7, which was first proposed in 1957[58] and is now generally accepted as the mechanism most consistent with the existing experimental data. The equilibrium for the initial electron addition must favor the left hand side because of the

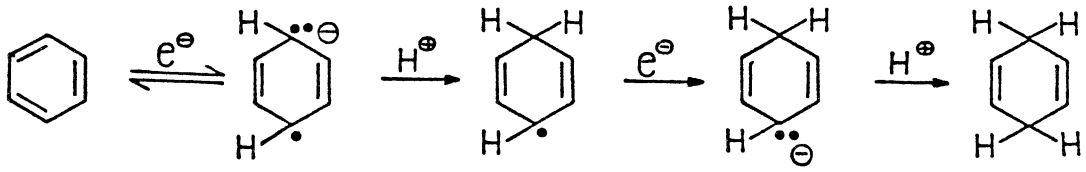


Figure 7. Radical Anion Mechanism for the Dissolving Metal Reduction of Monobenzenoid Compounds

unfavorable resonance energy change involved in the formation of the radical anion, and no reaction can ensue unless this intermediate is rapidly and irreversibly protonated.[13,14,59,64-68] The existence of radical anions has been demonstrated by electron spin resonance (ESR) studies of the alkali metal reduction of alkyl[69-73] and alkoxy[72,74,75] benzenes.

Rationalization of the formation of the deoxygenated, dihydro product 48, shown in Figure 5, requires that the radical anion 58 be protonated at C-2. Due to the low energy of activation for protonation of a radical anion, the species will presumably protonate most rapidly at the position of greatest charge accumulation.[67] This suggests that C-2 of 5a, a ring carbon with two ortho pi-donor substituents, is the position of greatest electron density. This is not an unreasonable occurrence and can, in fact, be predicted to a limited degree by careful consideration of the results obtained in earlier studies on the protonation

of the initial radical anion of substituted benzenes, particularly alkoxy benzenes. The protonation of the radical anion derived from anisole has been suggested to occur either ortho or meta to the alkoxy substituent as shown in Figure 8.

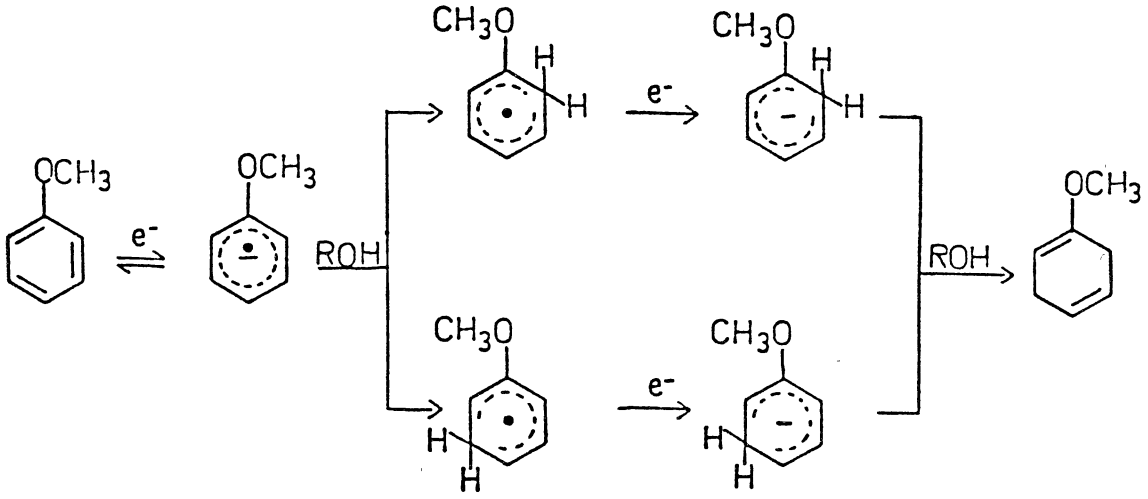


Figure 8. Mechanism for the Reduction of Anisole

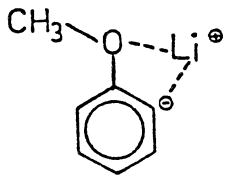
Ortho protonation has been argued by Zimmerman.[67] LCAO molecular orbital calculations yielded a prediction of electron distribution in radical anions derived from simple alkylated and methoxylated benzenes. The calculations predict that the electron density of such species is greatest at positions ortho to the substituent with the electron density increasing with an increasing number of such substituents. Ring carbon atoms meta to the methoxy (or

alkyl) group were found to be less electron rich while positions *para* were seen to have an even lower electron density. Ring carbon atoms bearing a pi-electron donor substituent were also shown to have a dramatically lower electron density.

On the other hand, *meta* protonation has been supported by Birch[57] and others[14,59] for the reason that the pi-electron donor substituent opposes the accumulation of charge in the *ortho* and *para* positions and therefore causes a high unpaired electron density in the *meta* positions. ESR studies have shown that the largest spin density does indeed occur at the *meta* positions of the toluene[69,70] and anisole[74,75] radical anions. Burnham,[66] who used calculated transition-state energies, also favors initial protonation at the *meta* position.

In a series of recent articles on the theoretical approach to the Birch reduction,[76] calculated molecular electrostatic potentials suggest that the kinetically preferred sites of protonation for the radical anions are *ortho* or *meta* for pi-electron donor substituents.[76b] The results of these studies do not indicate a strong preference for one or the other of these sites. *Ab initio* molecular orbital calculations[76c] predict, however, that the thermodynamically prefered site of protonation of a substituted benzene radical anion (corresponding to the most stable substituted cyclohexadienyl radical isomer) occurs *ortho* to a strong pi-donor (OH, OCH_3, and NH_2) and CH_3.

Ortho protonation of the radical anion of anisole may also be argued for on the basis that an accumulation of charge at the ortho postion may be stabilized as shown below.[77] Such a structure is similar to the intermediate



coordinated species formed during ortho lithiation of anisole.[78] It has also been suggested [11] that at the ortho position, there occurs a hyperconjugation which stabilizes the charge by transferring it partially to the carbon of the methoxy group. With alkyl groups, a stabilizing contribution of the same kind, although less pronounced, may occur.[11]

Returning again to Figure 5, the fate of radical anion 58 is thus determined by its environment. The reaction may proceed through dealkylation or deoxygenation, depending upon the presence or absence of a suitable proton source. In the presence of a proton source other than ammonia, such as an alcohol, 58 is protonated to 60 as has been described. A methoxy group is subsequently eliminated at C-2 to give 3-methylanisole (61). If a sufficient supply of electrons remains, 61 may be reduced to the dihydro product 48 indicated in Figure 5. Using a stoichiometric amount of lithium, 61 has been detected in the reaction mixture. This fact substantiates this route of the mechanism.

In the absence of a proton source, a methyl carbanion is expelled from the radical anion 58 to generate 59. Addition of another electron to 59 followed by aromatization gives a phenoxide which is resistant to further reduction. Subsequent protonation of the phenoxide gives 5b.

In the absence of a protonating agent, dealkylation prevails. However, in the presence of a suitable proton source, the alternate, deoxygenation route competes and becomes the prevalent course of reaction. This trend is demonstrated by the change in product (neutral/phenolic) ratios upon variation of the acidity of the alcoholic proton source in the lithium/ammonia reduction of 5a as shown in Table VI.

The arguments cited[67,76,77] to support the sequence in Figure 5, and the reaction sequence itself, can also be used to explain the lack of demethylation and demethoxylation in 45. Since the methoxy groups in 45 are situated *para* to each other, the electron density of the initial radical anion will be lowest at both of the methoxy substituted ring carbons. Hence, the possibility of dealkylation and/or deoxygenation of either methoxy group is at a minimum.

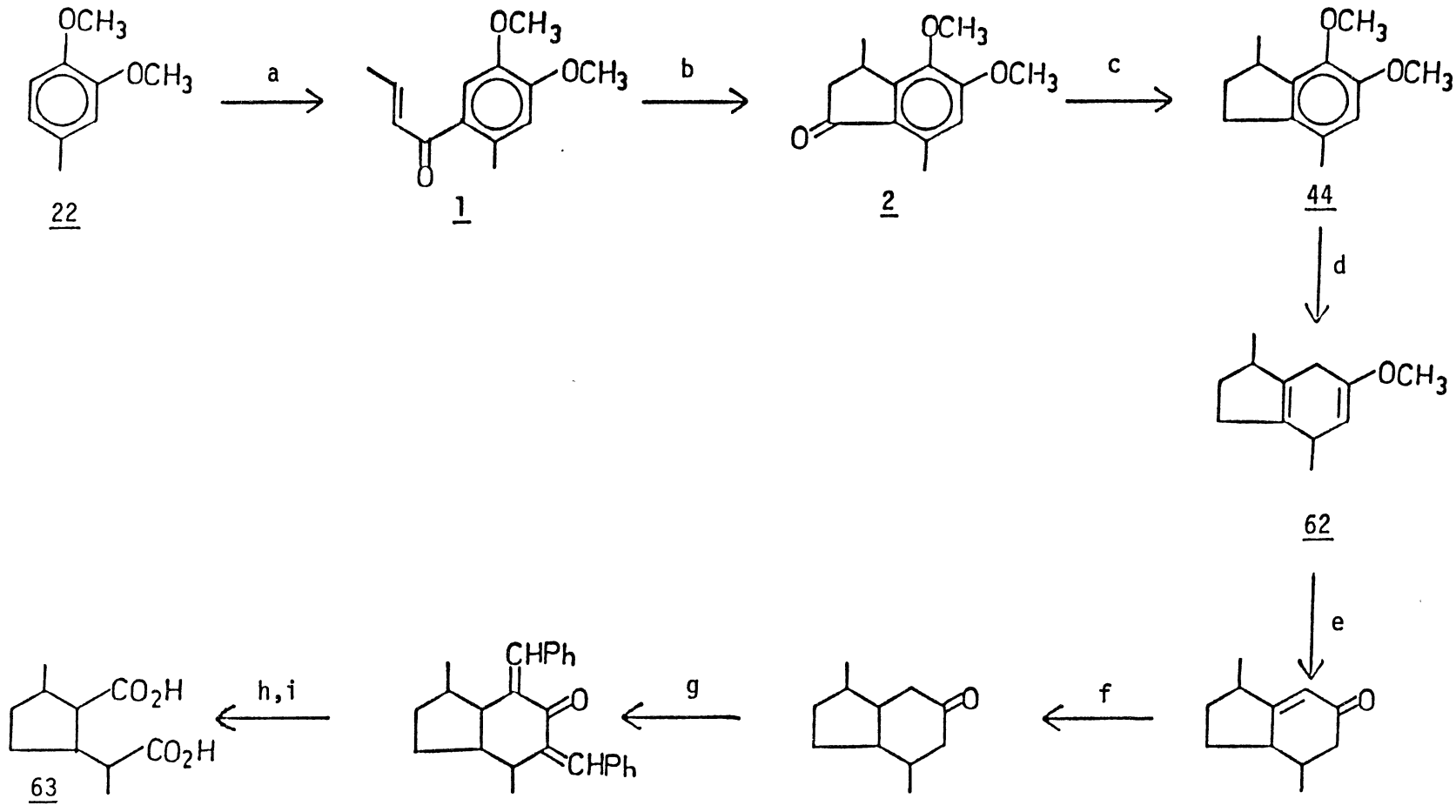
Synthetic Application

The initial goal of the author was the synthesis of nepetalinic acid (63). The originally conceived synthetic route, however, was eventually abandoned when a crucial conversion in the sequence could not be successfully carried

out. This necessitated the design of an alternate synthetic route for 63. The proposed route, outlined in Figure 9, employs a selective, reductive deoxygenation step which prompted the previously described study on the dissolving metal reductions of 3-substituted-1,2-dimethoxybenzenes.

The success of the route is contingent upon the conversion of 44 to 62. Compound 44 was prepared by a previously described[1,2a] multistep route starting from 22. Contrary to earlier reports, however, the cyclization of 1 with Amberlyst XN-1010[79] in refluxing chlorobenzene does not yield 2 as the exclusive product, although it is the major product (23.9% yield). Some cleavage to the keto phenol 3 occurs during the cyclization (1.0% yield). Subsequent hydrogenation of 2 in the presence of Pd/C gave 44 in excellent yield (96.0% yield).

The reduction of 44 with lithium/ammonia-ethanol failed to produce 62. Starting material was recovered quantitatively. This result was not entirely unexpected since the molecule is highly substituted with electron donor substituents. It was also believed that deoxygenation of the methoxy group at C-7 would be difficult due to the *para* methyl group at C-4. In spite of these arguments against the successful conversion of 44 to 62, the reduction was again attempted. The Wilds and Nelson[33a] procedure for hard to reduce compounds was tried. This method gave 40% starting material, 10% of 1,4-dimethyl-7-hydroxy-6-methoxyindan (64), and 18-20 other reduction products as evidenced by gas



[a]Crotonic acid, PPA, heat. [b]Amberlyst XN-1010, chlorobenzene. [c]Pd/C, H_2, HOAc. [d]Li/NH_3/EtOH. [e]H^+. [f]Pd/C, H_2. [g]C_6H_5CHO, NaOH. [h]CH_2Cl_2, O_3. [i]H_2O_2, NaOH.

Figure 9. Synthesis of Nepetalinic Acid (63)

chromatographic analysis of the acid treated reaction mixture. Several other attempts in which the metal concentration and the amount of proton source were altered were also tried resulting in similar mixtures.

Although the synthesis of 63 via the reaction sequence shown in Figure 9 has been detered due to this difficulty in the conversion of 44 to 62, the suggested synthetic route has provided us with the opportunity to investigate further the unique regiochemistry exhibited by sterically hindered aromatic methoxy groups.

CHAPTER III

EXPERIMENTAL

General Information

Proton NMR spectra were recorded on a Varian XL-300 spectrometer (at 299.944 MHz) or at 100.1 MHz on a Varian XL-100A instrument in the specified deuterated solvent with tetramethylsilane as an internal standard. The ^{13}C-NMR spectra were obtained at 75.429 MHz in the FT mode on a Varian XL-300 instrument or at 25.2 MHz in the FT mode on a Varian XL-100A interfaced with a 12 K Nicolet 1080 computer system with tetramethylsilane or deuterated chloroform as internal standard. Gas chromatographic analyses were performed on a Micro Tek 220 instrument using a 6' x 1/4", U-shaped, glass column packed with 5% Carbowax 20M on acid washed G Pak.

^{17}O-NMR Studies

The measurements were made with the ^{17}O nuclei in natural abundance (0.037%) on a Varian XL-300 spectrometer at 40.662 MHz in the FT mode. Samples were 60% (v/v) solutions in deuterated chloroform, in 5 mm tubes, at ambient temperature. The spectral settings were as follows: 25 KHz spectral width, 5000 data points, 16.5 μs or 20 μs

pulse width, 0.1 s acquisition time with no acquisition delay, 500,000 scans, and 30 Hz line broadening. Chemical shifts are expressed in ppm relative to the oxygen of water when measured in a capillary tube placed concentrically within a sample tube of 5 mm o.d..

The following compounds for study were available from previous work[2a,4] or were commercially available: 4a, 5a, 7, 35, 37-42, 44, and 45. 3-Ethyl-1,2-dimethoxybenzene (43) and 3-isopropyl-1,2-dimethoxybenzene (6a) were prepared as follows.

Preparation of 1-(2,3-Dimethoxyphenyl)-1-ethanol (65). In a 500 mL, three-necked flask were placed a Teflon-coated magnetic stirring bar and 190 mL (0.51 mol) of methylmagnesium bromide (Aldrich, 2.7 M in ether). To this solution, under nitrogen,[80] was added dropwise over a 2 h period and at ice bath temperature a solution of 77.5 g (0.47 mol) of 2,3-dimethoxybenzaldehyde in 200 mL of anhydrous ether. After addition was complete, the ice bath was removed and the mixture was refluxed for 2 h and subsequently decomposed with a solution of ammonium chloride and ice. The ether layer was separated and the remaining aqueous layer was extracted twice with ether. The combined ether extracts were washed with water, dried ($MgSO_4$), filtered, concentrated, and Kugelrohr distilled to give 74.9 g (88.1%) of 1-(2,3-dimethoxyphenyl)-1-ethanol (65); ^{1}H-NMR ($CDCl_3$) δ 1.40 (d, 3, CH_3), 3.76 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 4.04 (s, 1, OH), 5.12 (q, 1, CH), and 6.75-7.06 (m,

3, ArH); ^{13}C-NMR ($CDCl_3$) ppm 152.04, 145.35, 139.54, 123.96, 117.84, 111.06, 64.58, 60.49, 55.50, and 24.46.

Preparation of 3-Ethyl-1,2-dimethoxybenzene (43). A 7.0 g (0.039 mol) sample of alcohol 65, 1.4 g of 5% Pd/C, and 60 mL of glacial acetic acid were hydrogenated at 55 psi for 6 h. The mixture was cooled, filtered through Dicalite, and concentrated. The concentrate was diluted with 400 mL of water and then extracted with ether three times. The combined ether extracts were washed with a solution of sodium bicarbonate and separately with water, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to yield 5.25 g (90.8%) of 43 as a clear, colorless liquid; ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, 3, CH_3), 2.65 (q, 2, CH_2), 3.72 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), and 6.68-6.94 (m, 3, ArH); ^{13}C-NMR ($CDCl_3$) ppm 152.08, 146.45, 137.17, 123.16, 120.60, 109.59, 59.70, 54.85, 22.60, and 14.67; mass spectral data for $C_{10}H_{14}O_2$: m/e (M^+) 166.0990; found: 166.0994.

Preparation of 2,3-Dimethoxyacetophenone (66). A solution of 65.5 g (0.36 mol) of alcohol 65 in 300 mL of acetone was added to a 1 L, three-necked flask fitted with an addition funnel, thermometer, and high-speed mechanical stirrer. The solution was cooled to approximately 20 ^{o}C with an ice bath. The chromic acid oxidizing reagent (Jones reagent)[81] was then added dropwise such that the temperature of the reaction mixture did not increase substantially.

The course of the reaction was followed by GC. Samples of the reaction mixture were withdrawn at intervals,

decomposed with isopropyl alcohol, and injected directly into a GC. When all of the starting alcohol had been consumed, as evidenced by GC, and the reaction mixture was the dull orange color characteristic of the reagent, isopropyl alcohol was added dropwise until the excess chromic acid was destroyed. The volume of Jones reagent added over a 5 h period totaled approximately 100 mL.

The reaction mixture was filtered through Dicalite and the filter cake thoroughly rinsed with acetone. The acetone was permitted to evaporate and the solution then extracted with ether. The extract was washed with sodium bicarbonate, then with water, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to give 55.9 g (86.2%) of 2,3-dimethoxy-acetophenone (66); ^{1}H-NMR ($CDCl_3$) δ 2.60 (s, 3, CH_3), 3.76 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 7.02-7.20 (m, 3, ArH); ^{13}C-NMR ($CDCl_3$) ppm 199.72, 153.18, 148.78, 133.58, 123.95, 120.82, 116.01, 61.12, 55.94, and 31.16; mass spectral data for $C_{10}H_{12}O_3$: m/e (M^+) 180.0783; found: 180.0788.

Preparation of 1-(2,3-Dimethoxyphenyl)-1-methyl-1-ethanol (67). Into a 1 L, two-necked flask equipped with an addition funnel and Teflon-coated magnetic stirring bar was placed 125 mL (0.34 mol) of methylmagnesium bromide (Aldrich, 2.7 M in ether). The solution was cooled to ice bath temperature and a solution of the ketone 66 (54.0 g; 0.30 mol) in 250 mL anhydrous ether was added dropwise over a period of 1.75 h. After addition was complete, the thick suspension was stirred at room temperature for 1.5 h. The

reaction mixture was decomposed with a solution of ammonium chloride and ice, and the layers were separated. The aqueous layer was extracted twice more with ether. All ether extracts were combined, washed with water, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to yield 49.1 g (83.5%) of 1-(2,3-dimethoxyphenyl)-1-methyl-1-ethanol (67) as a colorless, viscous liquid; ^{1}H-NMR ($CDCl_3$) δ 1.55 (s, 6, CH_3), 3.70 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 4.38 (s, 1, OH), and 6.72-7.02 (m, 3, ArH); ^{13}C-NMR ($CDCl_3$) ppm 152.82, 146.63, 141.63, 123.51, 118.09, 111.68, 72.49, 60.58, 55.58, and 30.75.

Preparation of 3-Isopropyl-1,2-dimethoxybenzene (6a). Alcohol 67 (10.0 g; 0.05 mol) was hydrogenated in 75 mL of glacial acetic acid, using 1.0 g of 10% Pd/C, at 55 psi for 6 h. The mixture was cooled, filtered through Dicalite, and concentrated. The concentrate was poured into 600 mL of water and extracted with ether three times. The extracts were combined, washed with sodium bicarbonate, washed with water, dried ($MgSO_4$), and concentrated to give 8.6 g (93.6%) of 6a. The compound was further purified by Kugelrohr distillation; ^{1}H-NMR ($CDCl_3$) δ 1.32 (d, 6, CH_3), 3.50 (m, 1, CH), 3.86 (s, 3, OCH_3), 3.92 (s, 3, OCH_3), and 6.80-7.14 (m, 3, ArH); ^{13}C-NMR ($CDCl_3$) ppm 152.10, 145.90, 141.56, 123.31, 117.56, 109.27, 59.79, 54.68, 26.24, and 22.83; mass spectral data for $C_{11}H_{16}O_2$: m/e (M^+) 180.1146; found: 180.1139.

Dissolving Metal Reduction Studies

General Procedure for the Reduction of Aromatic Ethers. All reactions were carried out in oven-dried glassware under an inert atmosphere of prepurified argon. The reductions were conducted in a 250 mL, three-necked flask equipped with a polypropylene-coated magnetic stirring bar, Dry Ice-reflux condenser, and adapter inlets for ammonia and argon gases. As necessary, a Dry Ice-acetone bath was used for external cooling of the reaction vessel.

The substrate, alcohol, and solvent (if necessary) were placed in the reaction vessel and stirred to achieve solution. The desired amount of anhydrous ammonia was distilled into the reaction vessel, after which lithium was introduced, in small portions, through Gooch tubing attached to one of the ports of the flask. Upon completion of the addition, the external cooling bath was removed and the reaction mixture was stirred under reflux until the characteristic blue color of metal-ammonia solutions had disappeared. The condenser was removed and the ammonia was allowed to evaporate. Cold water was carefully added to the reaction mixture and the product was extracted into ether, washed with water, and concentrated. To isolate the base-soluble products, the aqueous layer was carefully acidified with dilute hydrochloric acid prior to its extraction with ether. The ether layer was washed with water, dried ($MgSO_4$), and concentrated.

Lithium/Ammonia-Alcohol Reduction of 3-Methyl-1,2-dimethoxybenzene (5a). A. The aromatic ether 5a (3.0 g; 0.02 mol) was reduced with 0.9 g (0.13 mol) of lithium, approximately 100 mL of freshly distilled ammonia, and 32 mL (0.34 mol) of anhydrous (distilled over CaH_2) tert-butyl alcohol in 20 mL of anhydrous ether[82] according to the general procedure for reduction. Two fractions were collected upon work up, 1.22 g of a pale-yellow liquid containing base-insoluble materials and 0.45 g of a dark-brown, base-soluble liquid which solidified upon standing.

GC analysis of the base-insoluble material revealed one predominant (95% of the fraction, 44% overall yield) product which was identified by ^{1}H- and ^{13}C-NMR as 48: ^{1}H-NMR ($CDCl_3$) δ 1.70 (s, 3, CH_3), 2.60 (t, 2, CH_2), 2.78 (m, 2, CH_2), 3.54 (s, 3, OCH_3), 4.64 (s, 1, vinyl H), and 5.42 (s, 1, vinyl H); ^{13}C-NMR ($CDCl_3$) ppm 153.016 (s), 121.235 (s), 118.858 (d), 90.311 (d), 53.769 (q), 33.280 (t), 26.936 (t), and 22.862 (q); mass spectral data for $C_8H_{12}O$: m/e (M^+) 124.0885; found: 124.0877. The identity of 48 was confirmed by mineral acid hydrolysis (dilute hydrochloric acid) to the unsaturated ketone 3-methyl-2-cyclohexen-1-one (49). Ketone 49 gave a derivative with 2,4-dinitrophenylhydrazine as dark red plates, mp 169 °C (lit[10a] 173 °C). A minor component (4% of the fraction) of the base-insoluble fraction was tentatively identified as 1,4-dihydro-2,3-dimethoxytoluene (50) based on the assignment of signals in the NMRs obtained

on the fraction: ^{1}H-NMR ($CDCl_3$) δ 1.16 (d, 3, CH_3), 2.84 (m, 3, allylic H), 3.63 (s, 3, OCH_3), 3.66 (s, 3, OCH_3), and 5.54 (m, 2, vinyl H); ^{13}C-NMR ($CDCl_3$) ppm 154.396 (s), 153.027 (s), 130.510 (d), 130.446 (d), 58.267 (q), 56.969 (q), 33.503 (t), 28.231 (d), and 19.755 (q).

The base-soluble material was shown by GC analysis to consist of two components in a 95:5 ratio. Comparison of the ^{1}H-NMR and ^{13}C-NMR of the mixture along with the retention times of the individual components of the mixture with those obtained on authentic samples of 2-methoxy-6-methylphenol (5b) and 2-methoxy-3-methylphenol (5d) showed these two phenols to be present in the mixture. The major isomer was established as 5b.

B. tert-Butyl alcohol was substituted with ethanol (20 mL; 0.34 mol) in the reduction of 5a (3.0 g; 0.02 mol) with 0.9 g (0.13 mol) lithium and 100 mL ammonia. During customary work up, base-insoluble (1.20 g) and base-soluble (0.10 g) materials were collected. The products obtained were found to be identical to those (48, 50, 5b, 5d) in the previous experiment. The product ratios and yields are presented in Table VI.

C. Reduction of 5a (3.0 g; 0.02 mol) using methanol (13.8 mL; 0.34 mol) as the proton source yielded, upon work up, 1.75 g of base-insoluble material and 0.09 g of phenolic material. The components of each fraction were similar to those previously obtained.

D. Using isopropyl alcohol (26 mL; 0.34 mol), 2.15 g of product material was obtained in the reduction of 0.02 mol (3.0 g) of 5a. Of the entire amount, 1.9 g was base-insoluble matter.

E. 2,2,2-Trifluoroethanol (12 mL; 0.17 mol) was used in the reduction of 0.01 mol (1.5 g) of 5a with lithium and ammonia (100 mL). Rapid evolution of hydrogen occurred upon addition of the lithium to the solution of substrate, ammonia, proton source, and diethyl ether. The characteristic dark blue color did not form. Starting material was recovered quantitatively.

F. Freshly distilled 3-ethyl-3-pentanol (23.8 mL; 0.17 mol) served as the proton source in the lithium (0.45 g; 0.065 mol)/ammonia (50 mL) reduction of 0.01 mol of 5a. The solution required 8.5 h of stirring at -78 ^{o}C and 1 h of stirring at reflux temperature for the blue color of the reaction mixture to vanish. As usual, a base-insoluble fraction (20.05 g) and a base-soluble fraction (0.67 g) were collected during work up.

GC analysis of the base-insoluble material indicated that 97.5% of the fraction (19.5 g) was 3-ethyl-3-pentanol which could not be separated from the product material by base extraction or distillation. Of the actual product material, the major component (95% of the material) had a retention time corresponding to that of 48. The phenolic fraction was determined to contain 5b and 5d.

G. Aromatic ether 5a (6.6 g; 0.043 mol) was reduced with a limited amount of lithium (0.6 g; 0.086 mol), approximately 150 mL of ammonia, and 10 mL of absolute ethanol in ether (15 mL) according to the general procedure for reduction. Two fractions were again collected upon work up: 4.90 g of base-insoluble and 0.06 g of phenolic materials.

The base-insoluble matter was refluxed with dilute hydrochloric acid for 1 h and then brought to room temperature. The mixture was taken up in ether, washed with water, dried ($MgSO_4$), concentrated, and subjected to GC analysis. This revealed the presence (by comparison of retention times with authentic samples) of starting material (86% of fraction), ketone 49, 3-methylanisole (61), and 2-methylanisole (38). The ratio of the latter two components was determined to be 4:1 by GC. MS of the mixture confirmed the presence of starting material (m/e (M^+) 152.0834; found: 152.0826), ketone 49 (m/e (M^+) 110.0729; found: 110.0689), and $C_8H_{10}O$ (m/e (M^+) 122.0331; found: 122.0601).

Phenols 5b and 5d were identified to be the only components in the base-soluble fraction in a ratio of 95 to 5, respectively.

Lithium/Ammonia Reduction of 3-Methyl-1,2-dimethoxybenzene (5a). A. Ether 5a (3.0 g; 0.02 mol) was reduced with 0.13 mol of lithium and ammonia (100 mL) according to the general procedure for reduction. However, no alcohol was added. The dark blue solution was permitted to stir at

reflux temperature for 2.5 h after completion of addition of the lithium. Following reflux, the excess lithium was consumed by the careful addition of saturated ammonium chloride. The ammonia was allowed to evaporate.

Two fractions were collected. The base-insoluble fraction (0.33 g) was predominantly composed of unreacted starting material (93% of the fraction, 10% overall yield), as determined by GC. Similar to previous reductions of this compound, 5b and 5d were determined to be the components of the phenolic fraction, 5b being the major isomer. The total combined yield of phenols was 72%.

B. Similar reduction of 3.0 g (0.02 mol) of 5a without an added proton source was carried out. The reaction, however, was quenched with water. Essentially only phenolic material was isolated (2.4 g, 87% total yield). Phenols 5b and 5d were formed in a ratio of 96 to 4, respectively.

Reduction of 4-Methyl-1,2-dimethoxybenzene (22). A. Lithium metal (0.9 g; 0.13 mol), approximately 100 mL of ammonia, and 20 mL (0.34 mol) of ethanol in 20 mL of anhydrous ether were used in the reduction of 22 (3.0 g; 0.02 mol). A pale-yellow, base-insoluble fraction (1.82 g) was collected, in addition to 0.02 g of phenolic material. Separation of these fractions into individual components was not successful. Identification of the major species of each fraction was accomplished via ^{1}H- and ^{13}C-NMR and MS.

The major component (88% of the fraction) of base-insoluble material was identified by ^{1}H-NMR to be 24:

^{1}H-NMR ($CDCl_3$) δ 1.90 (s, 3, CH_3), 2.27-2.88 (unresolved m, 4, allylic H), 3.62 (s, 3, OCH_3), 3.64 (s, 3, OCH_3), and 5.30 (broad s, 1, vinyl H); mass spectral data for $C_9H_{14}O_2$: m/e (M^+) 154.0990; found 154.1001.

GC analysis of the phenolic fraction showed two components in an approximate 60:40 ratio. These were identified as 53 and 54, respectively, by comparison of the ^{1}H- and ^{13}C-NMR and GC retention times of authentic samples.

B. The experiment described in part A. was repeated using tert-butyl alcohol to give 1.65 g of base-insoluble material and 0.35 g of phenolic material. The products obtained were spectrally identical to those obtained above (24, 53, 54).

Reduction of 1,2,3-Trimethoxybenzene (35). Ether 35 (3.0 g; 0.018 mol) was treated with lithium (0.09 g; 0.13 mol) in 20 mL of anhydrous ether, 20 mL (0.34 mol) of ethanol, and 100 mL of distilled ammonia according to the general procedure. The major (95% of the fraction, 92% overall yield) base-insoluble component was 1,5-dimethoxy-cyclohexa-1,4-diene (36): ^{1}H-NMR ($CDCl_3$) δ 2.85-2.80 (unresolved m, 4, CH_2), 3.55 (s, 6, OCH_3), and 4.66 (m, 2, vinyl H); ^{13}C-NMR ($CDCl_3$) ppm 151.559, 90.1642, 53.5734, 30.7488, and 24.6796; mass spectral data for $C_8H_{12}O_2$: m/e (M^+) 140.0834; found: 140.0826.

Reduction of 4,5-Dimethoxyindan (7). Lithium (0.45 g; 0.065 mol), 100 mL of ammonia, and 10 mL (0.17 mol) of ethanol in 20 mL of ether were used in the reduction of 7

(1.8 g; 0.01 mol). Two fractions were collected during work up.

4,7-Dihydro-5-methoxyindan (8) was determined to be the major component (79% yield) of the base-insoluble material (1.25 g): ^{1}H-NMR ($CDCl_3$) δ 1.96-1.82 (p, 2, CH_2), 2.40-2.20 (m, 4, allylic H), 2.78-2.60 (m, 4, allylic H), 3.56 (s, 3, OCH^3), and 4.66 (broad s, 1, vinyl H); ^{13}C-NMR ($CDCl_3$) ppm 154.165, 132.298, 131.641, 90.971, 35.346, 30.134, 26.954, and 22.419.

The base-insoluble material was added to an aqueous solution of oxalic acid (0.5 g in 30 mL of water) and heated to reflux for 2.5 h. The cooled solution was extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to a dark-brown liquid. GC analysis of this liquid showed one major component which was established to be 51: ^{13}C-NMR ($CDCl_3$) ppm 199.833, 175.750, 122.005, 43.089, 37.418, 32.793, 31.849, 29.243, and 23.858; mass spectral data for $C_9H_{12}O$: m/e (M^+) 136.0885; found: 136.0798. Ketone 51 gave a derivative with 2,4-dinitrophenylhydrazine as dark red crystals, mp 194-196 °C (lit[10a] 197-198 °C).

The base-soluble material (0.02 g) contained predominantly one product. Spectral data matched those of an authentic sample of 4-hydroxy-5-methoxyindan (9).

Reduction of 4,5-Dimethoxyindanone (52). Indanone 52 (1.9 g; 0.01 mol) was reduced with 0.065 mol (0.45 g) of lithium, 100 mL of ammonia, and 10 mL of absolute ethanol in 50 mL of anhydrous ether. During the course of the reaction,

the solution underwent several color changes - from light-yellow to green to the characteristic blue of a Birch reduction, and finally, back to pale-yellow. A base-insoluble fraction (0.86 g) and a base-soluble fraction (0.03 g) were collected upon work up.

GC analysis of the largest fraction revealed approximately 15 species. The retention time of one of the components corresponded to that of 8 obtained previously. Separation and subsequent identification of the products proved unsuccessful. Phenol 9 was detected in the remaining fraction.

Reduction of 4-Methoxy-2,3,6-trimethylanisole (45). A. Compound 45 (1.0 g; 0.0055 mol) was reduced with 0.036 mol (0.25 g) of lithium, 50 mL of ammonia, and ethanol (6 mL; 0.01 mol) in 6 mL of ether as co-solvent according to the general procedure. Starting material was recovered.

B. To 45 (0.52 g; 0.0028 mol), dissolved in 30 mL of 1,2-dimethoxyethane (distilled from NaH and LAH), was added 100 mL of ammonia. Lithium (0.82 g; 0.117 mol) was added in portions. After stirring for 15 minutes, ethanol was added dropwise over a 15 minute period until the blue color had been discharged (17 mL). An additional 15 mL of ammonia and 0.54 g (0.077 mol) of lithium were added to the reaction mixture and the solution was stirred for another 10 minutes. More ethanol (3 mL) was added over 10 minutes to discharge the color. The reaction was worked up as described in the general procedure.

GC analysis of the base-insoluble material (0.43 g) indicated the presence of one major product and 8 or 9 minor ones, one of which was unreacted starting material (<1%). The major component (78%) was identified by NMR to be 55: ^{1}H-NMR ($CDCl_3$) δ 1.06-1.08 (d, 1, CH_3), 1.60 (s, 6, CH_3), 3.42 (s, 3, OCH_3), and 3.46 (s, 3, OCH_3); ^{13}C-NMR ($CDCl_3$) ppm 150.020, 144.579, 115.208, 110.973, 56.336, 55.664, 35.134, 31.238, 17.868, 14.702, and 12.700; mass spectral data for $C_{11}H_{18}O_2$: 182.1302; found 182.1309.

Reduction of 2,3-Dimethoxybenzoic Acid (56). A solution of 1.8 g (0.01 mol) of 56 in 10 mL of ether was reduced with 0.45 g (0.065 mol) of lithium, 10 mL of ethanol, and ammonia (100 mL) according to the general procedure for reduction. The product mixture was acidified with dilute hydrochloric acid, refluxed for 10 minutes, cooled, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated to 1.2 g (86%) of a pale-brown solid, mp 197-200 ^{o}C. Melting point, ^{1}H-NMR, ^{13}C-NMR, and MS data of this solid matched that acquired on an authentic sample of 3-hydroxybenzoic acid (57).

Preparation of 4',5'-Dimethoxy-2-methylcrotonophenone (1). Crotonic acid (172 g; 2.0 mol), followed by 304 g (2.0 mol) of 4-methyl-1,2-dimethoxybenzene (22), was added to 4920 g of PPA contained in a 12 L flutted flask fitted with a mechanical stirrer and thermocouple probe. The temperature of the solution was maintained at approximately 56 ^{o}C and stirring continued at this temperature for 3 h. During this

period a color change from pale-yellow to dark-brown was noted.

The viscous mixture was then poured onto ice water (6 L) and stirred. The brown solution was extracted with ether three times and the combined extracts were washed with saturated sodium carbonate twice and with water once. The ether was dried ($MgSO_4$), concentrated, and Kugelrohr distilled to give 270 g of a yellow oil which crystallized upon standing. Two recrystallizations from n-hexane gave 263.9 g (61.4%) of a pale-yellow solid, mp 61-62 °C. The product was shown by GC to be a mixture of 1 and 68, in an approximate ratio of 9:1, respectively. The products obtained were spectrally identical to those obtained by previous workers.[1,2a]

Preparation of 4,5-Dimethoxy-3,7-dimethyl-1-indanone (2). To a 5 L, three-necked flask equipped with a Teflon-coated magnetic stirring bar, Dean-Stark trap with reflux condenser, and thermometer were added 35 g (0.16 mol) of the mixture of crotonophenones 1 and 68 obtained in the previous section, 3.5 L of chlorobenzene, and 35 g of Amberlyst XN-1010. The reaction mixture was heated at reflux (130 °C) for 41 h until the starting material was consumed, as evidenced by GC. The dark mixture was then cooled, filtered, and concentrated to 27.9 g of black, viscous material. Kugelrohr distillation of this material gave 8.7 g of a yellow liquid containing predominantly 22. A yellow oil (9.3 g), which was shown by GC to consist of indanone 2 and

keto-phenol 3 in a ratio of 24:1 was also obtained. The oil was purified by passing through a soxhlet column containing a plug of basic alumina, neutral alumina, and ether as solvent. Concentration of the ether resulted in 8.4 g (23.9%) of 2 as confirmed by spectral data.

Preparation of 4,5-Dimethoxy-3,7-dimethylindan (44). A mixture of 2 (5.0 g; 0.023 mol), 90 mL of acetic acid, and 1.0 g of 5% Pd/C was hydrogenated at 50 psi until uptake of hydrogen had ceased. The cooled mixture was then filtered through Dicalite and concentrated. The concentrate was subsequently diluted with water and the products extracted into ether. The ether extract was washed with a solution of sodium bicarbonate and separately with water, dried ($MgSO_4$), and concentrated to 4.5 g (96.0%) of a pale-yellow solid, mp 50-52 ^{o}C. Spectral data and melting point of this material confirmed the identity as 44.

Reduction Attempts of 4,5-Dimethoxy-3,7-dimethylindan (44). **A.** Indan 44 (2.0 g; 0.01 mol), dissolved in 10 mL of ether, was reduced with lithium (0.45 g; 0.065 mol), ammonia (100 mL), and 10 mL (0.17 mol) of ethanol as proton source according to the general procedure for reduction. Starting material was recovered.

B. Indan 44 (2.55 g; 0.0124 mol) was dissolved in 25 mL of 1,2-dimethoxyethane, to which was added 0.60 g (0.09 mol) of lithium in small pieces over a period of 2 minutes. After stirring for 10 minutes, absolute ethanol (approximately 3 mL) was added dropwise over 17 minutes

until the blue color had been discharged. The ammonia was then allowed to evaporate.

The usual work up was performed. The base-insoluble fraction was immediately hydrolyzed with hydrochloric acid and the product subsequently extracted into ether, dried ($MgSO_4$), and concentrated to 2.2 g of brown liquid. GC analysis of this material revealed about 40% of starting material and 18-20 other peaks, the identities of which are not known. ^{13}C-NMR of this mixture, however, did indicate the presence of some ketonic material. The base-soluble fraction (0.05 g) was primarily phenol 64.

C. Method A. was repeated using sodium (1.5 g; 0.065 mol) in place of lithium for the reduction of 0.01 mol of 44. Starting material was recovered.

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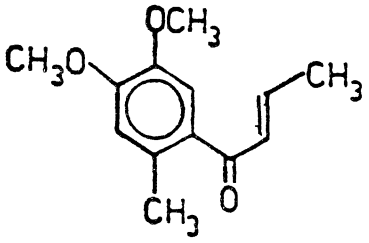
APPENDIX A

GLOSSARY OF STRUCTURES



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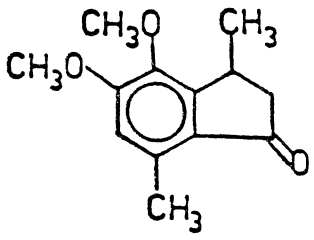

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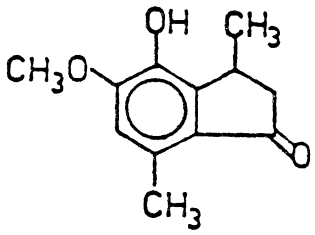

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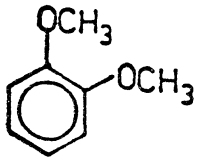

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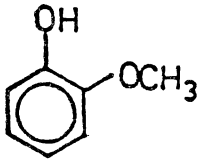

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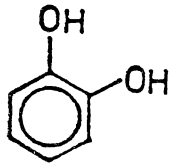

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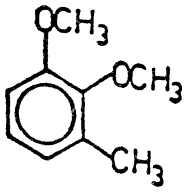

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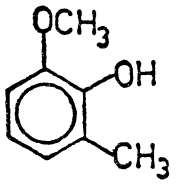

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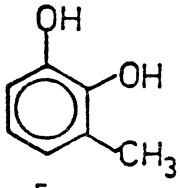

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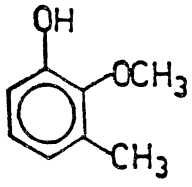

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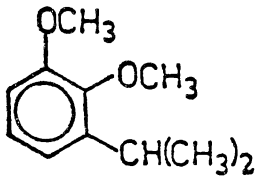

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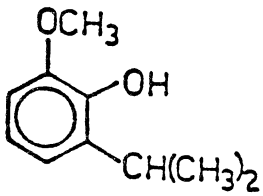

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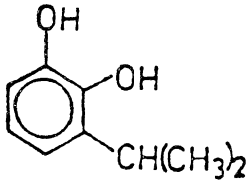

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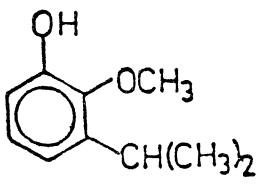

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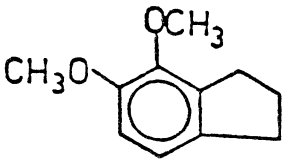

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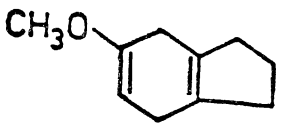

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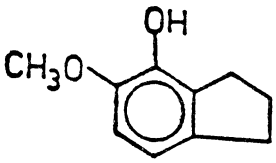

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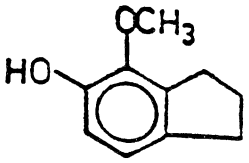

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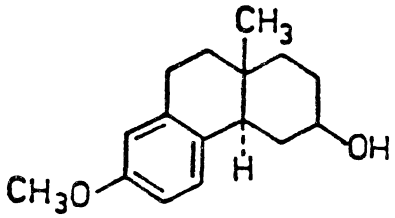

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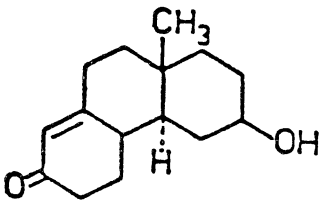

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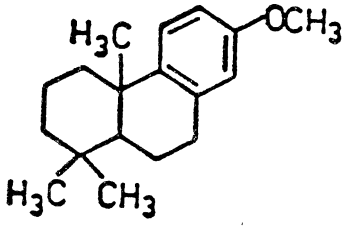

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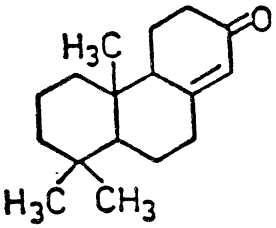

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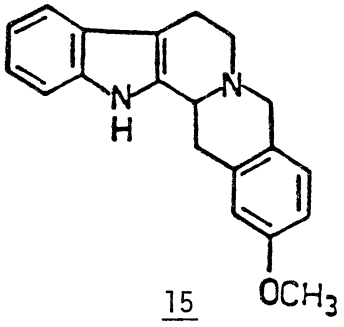

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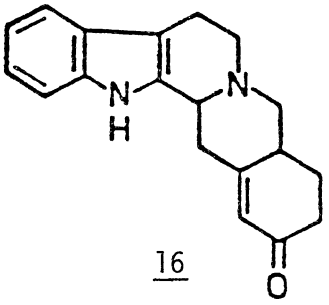

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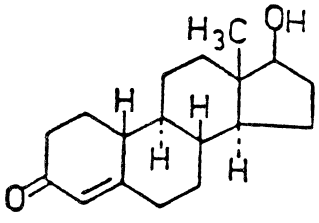

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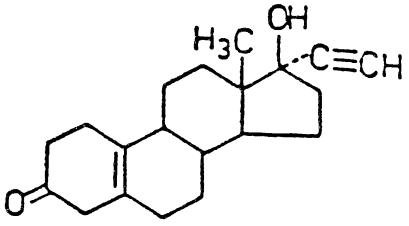

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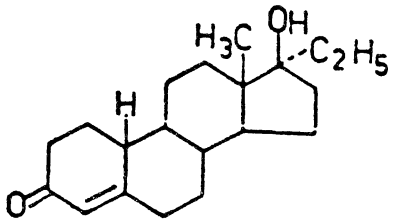

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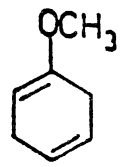

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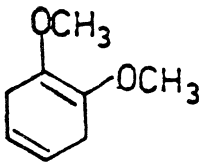

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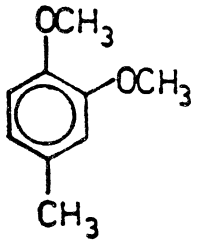

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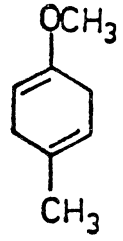

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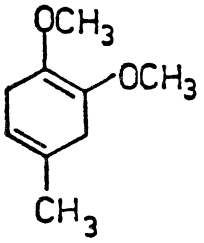

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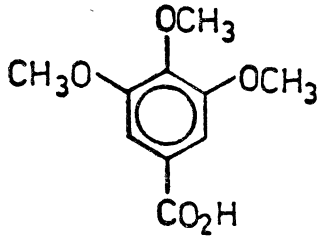

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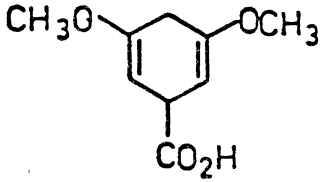

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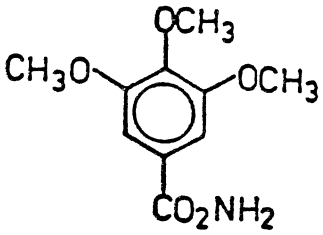

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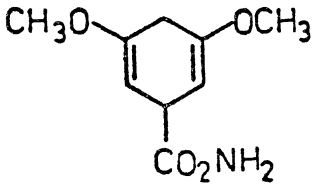

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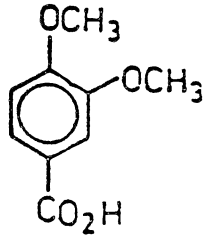

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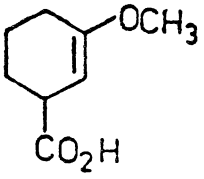

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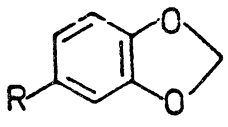

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b R=CO_2H
c R=H
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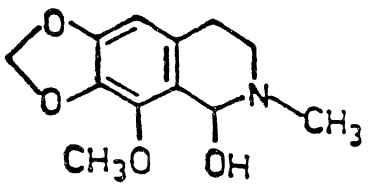

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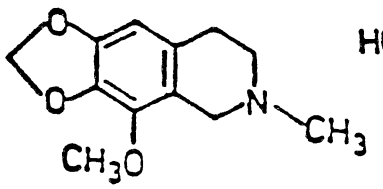

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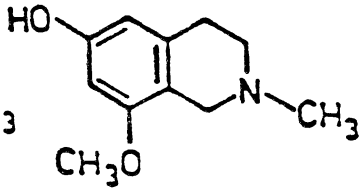

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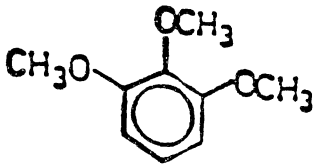

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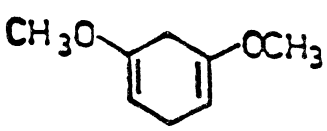

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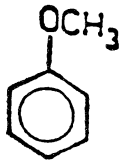

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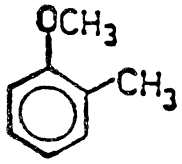

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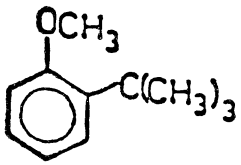

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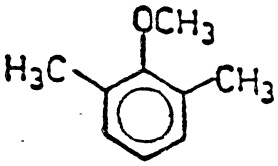

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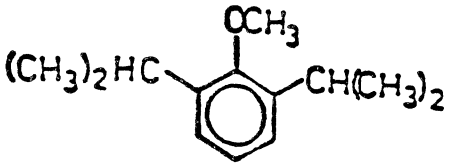

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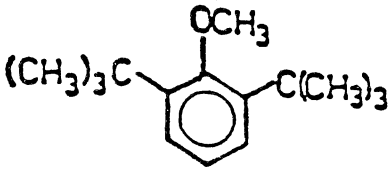

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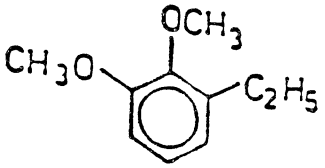

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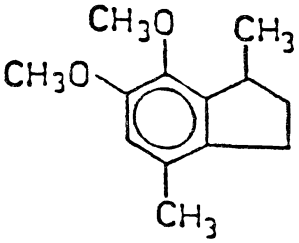

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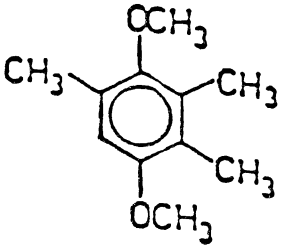

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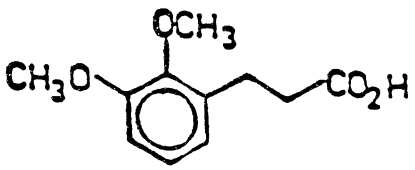

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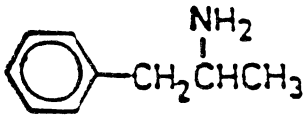

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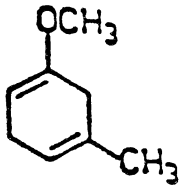

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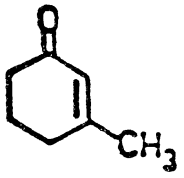

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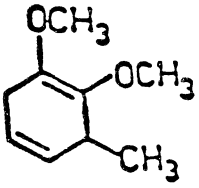

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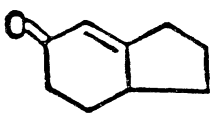

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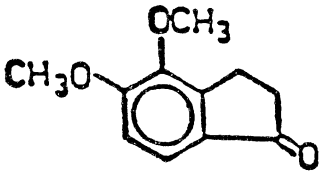

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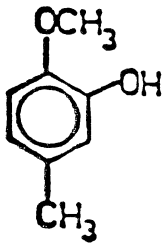

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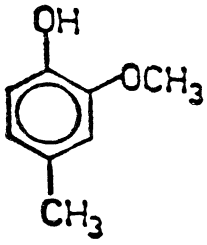

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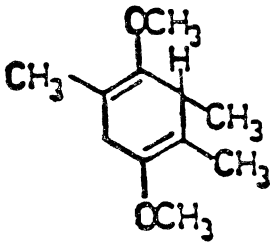

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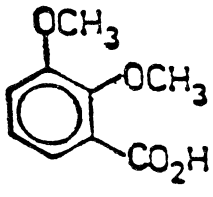

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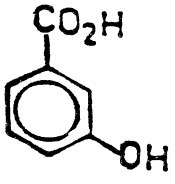

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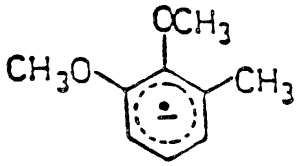

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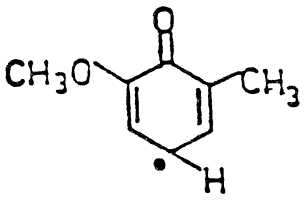

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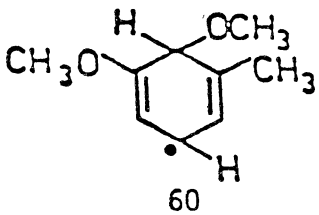

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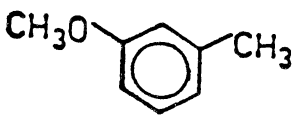

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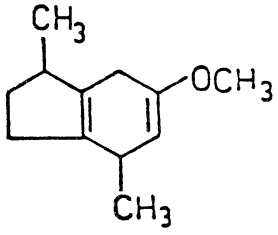

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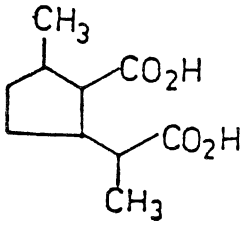

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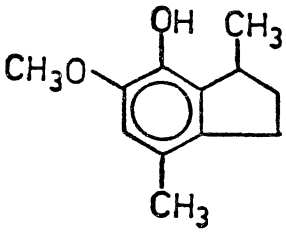

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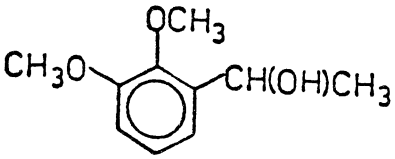

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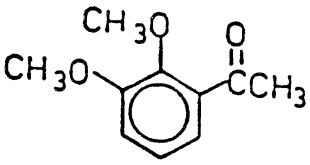

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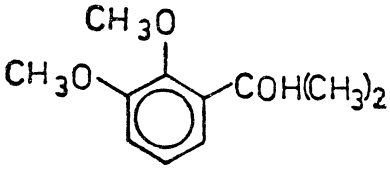

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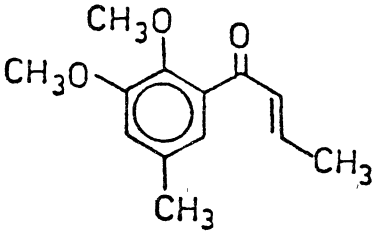

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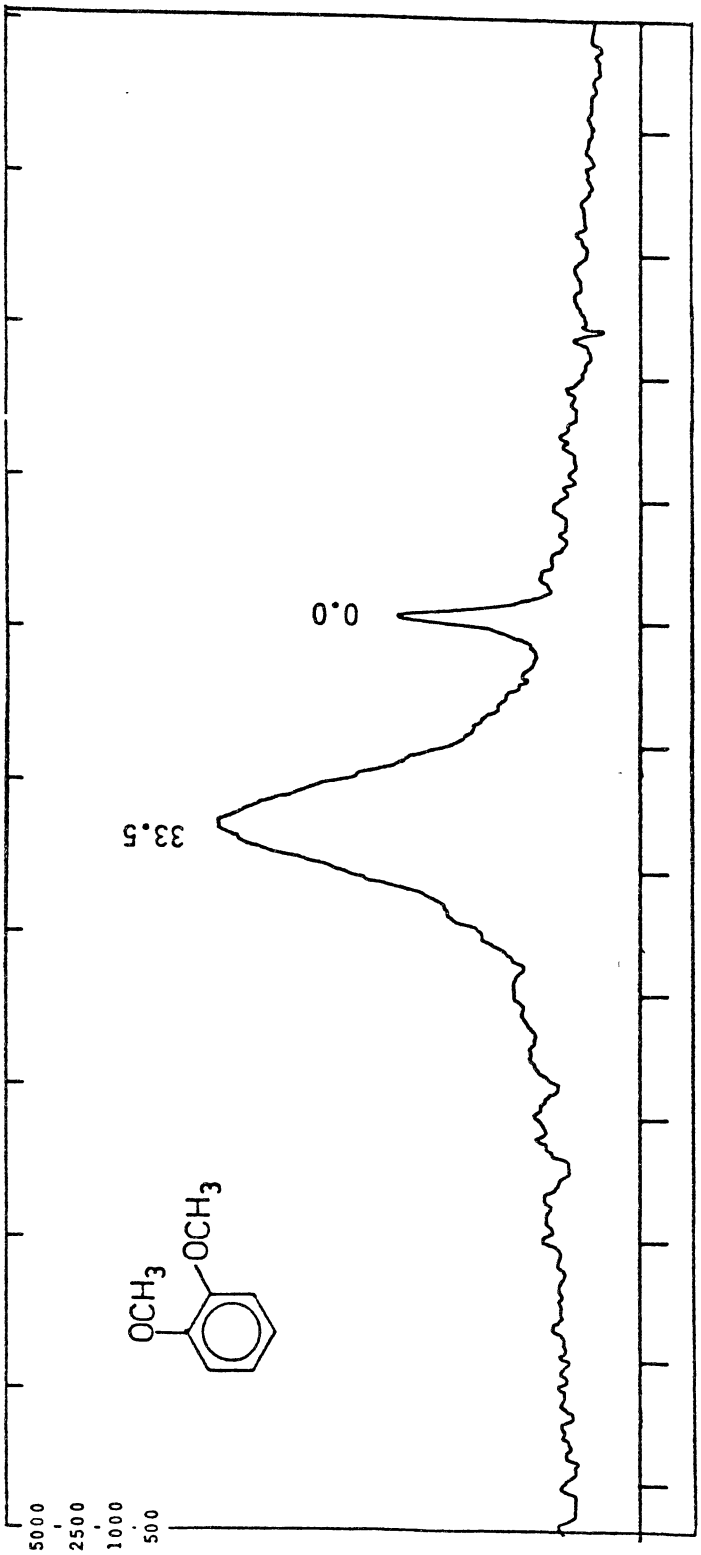
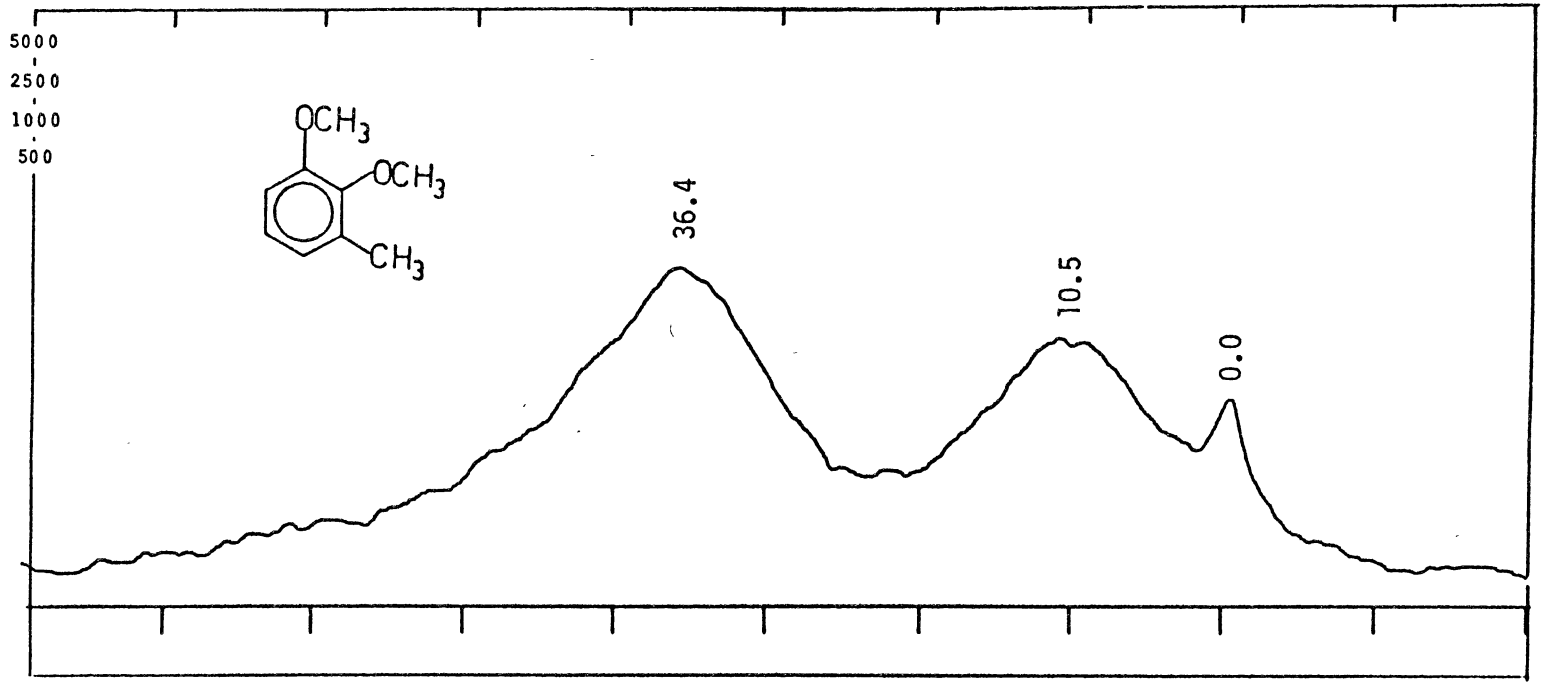
APPENDIX B

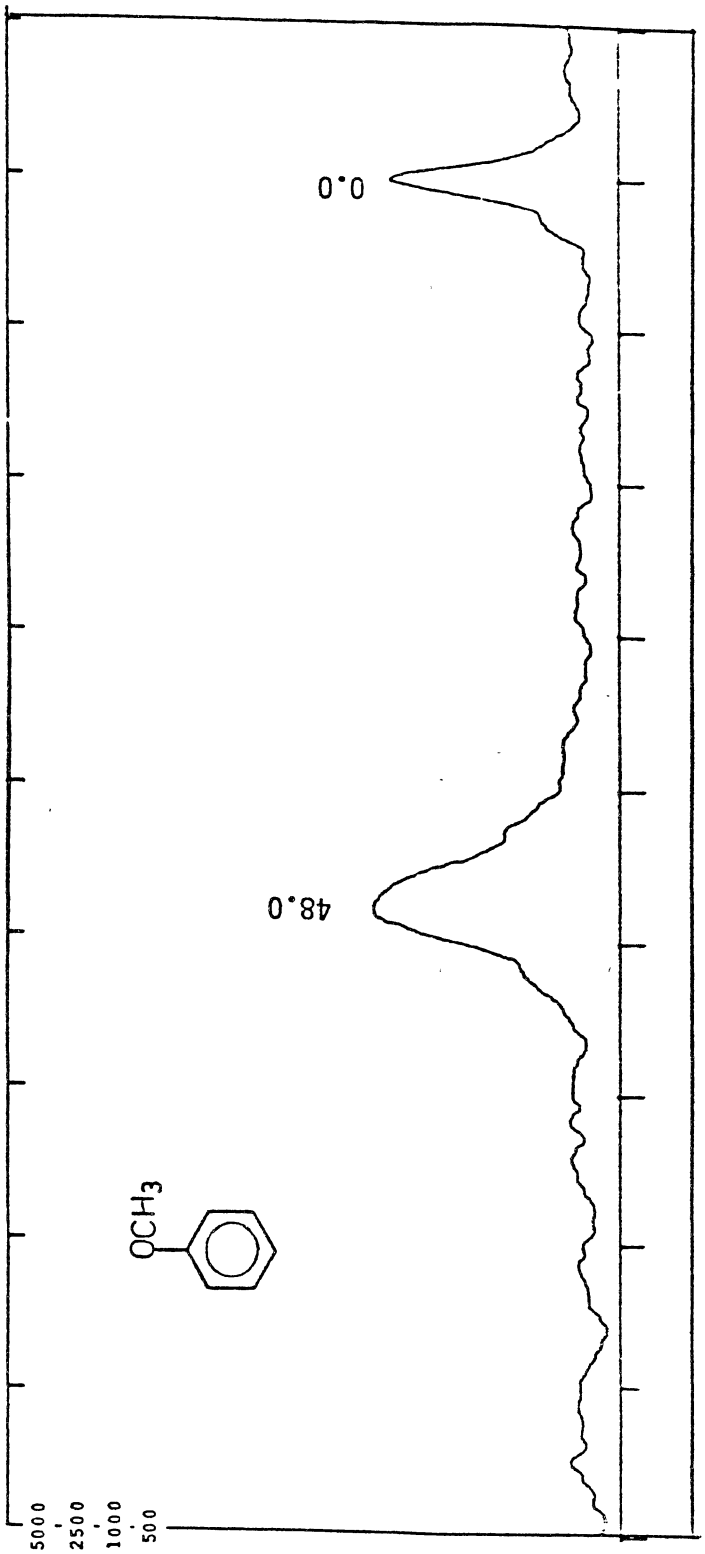
SELECTED ^{17}O-NMR SPECTRA



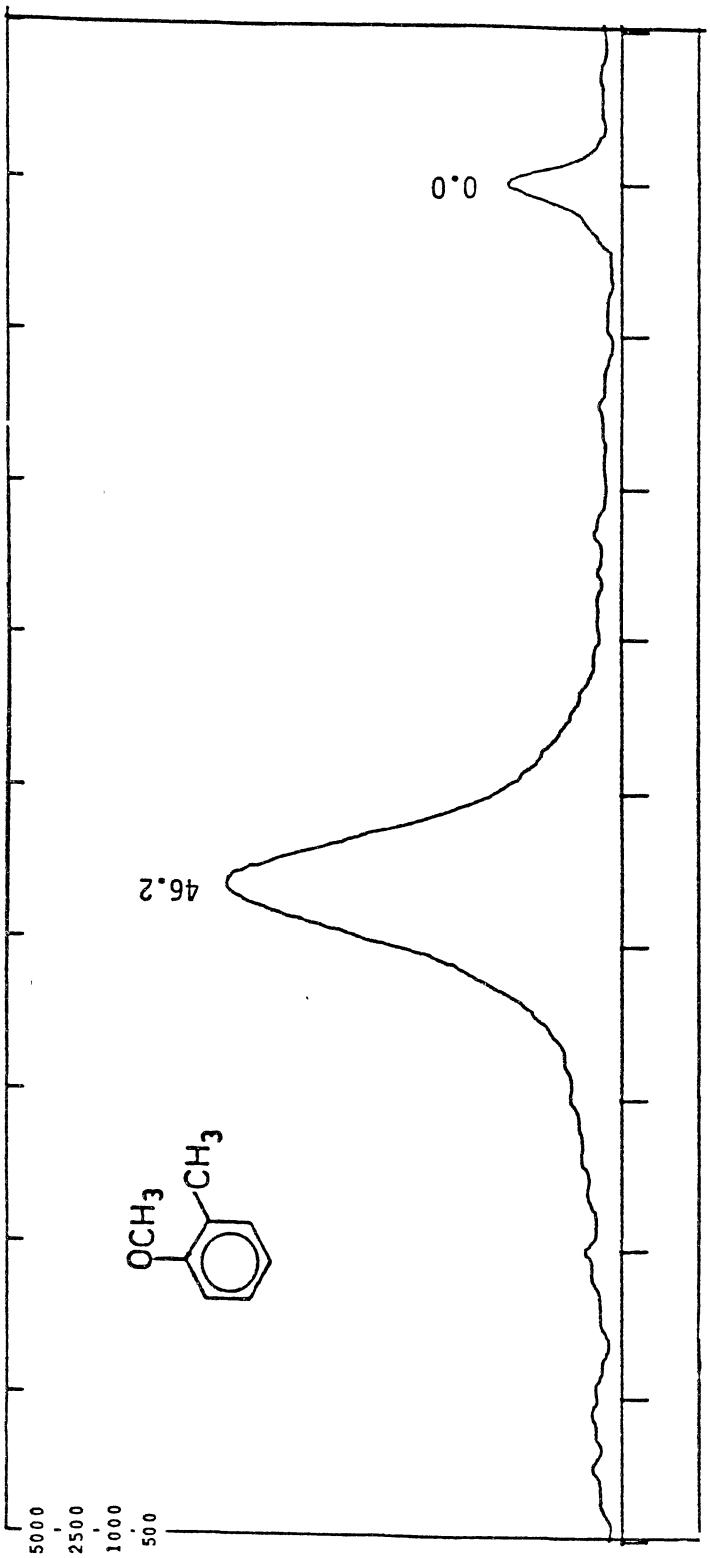
Spectrum 1. ^{17}O-NMR of 1,2-Dimethoxybenzene (4a)



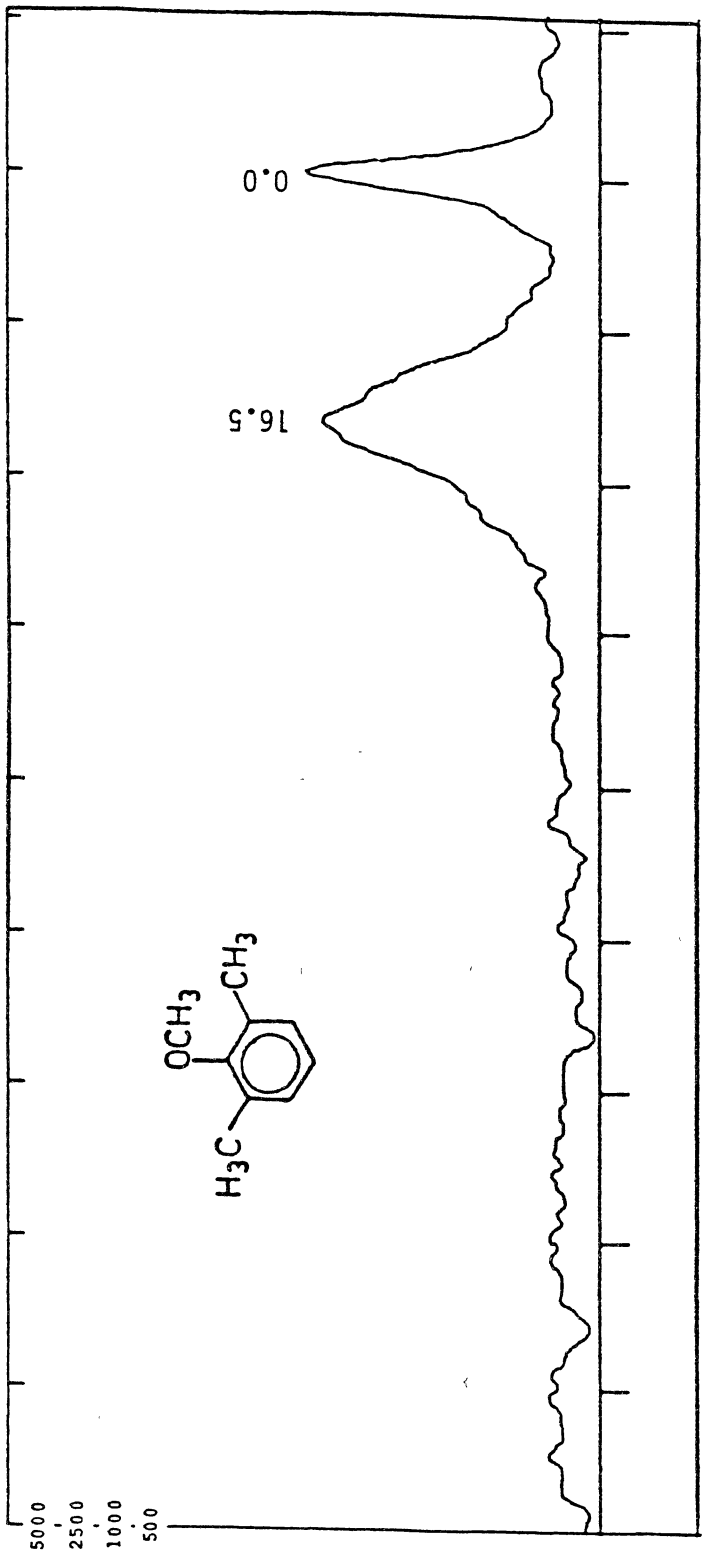
Spectrum 2. ^{17}O-NMR of 3-Methyl-1,2-dimethoxybenzene (5a)



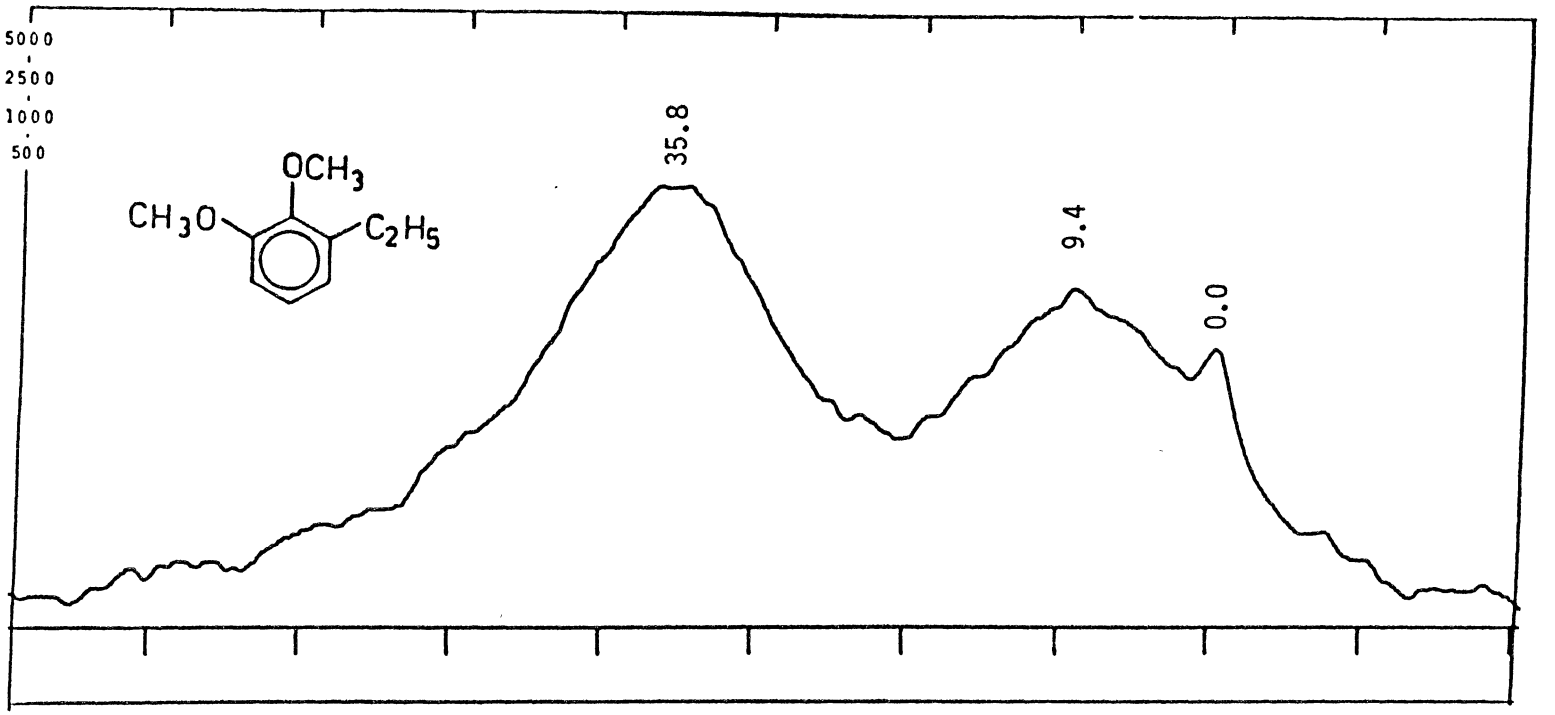
Spectrum 3. ^{17}O-NMR of Anisole (37)



Spectrum 4. ^{17}O-NMR of 2-Methylanisole (38)



Spectrum 5. ^{17}O-NMR of 2,6-Dimethylanisole (40)



Spectrum 6. ^{17}O-NMR of 3-Ethyl-1,2-dimethoxybenzene (43)

VITA 2

Monica Ann Wysocki

Candidate for the Degree of

Doctor of Philosophy

Thesis: THE CONFORMATION AND REGIOCHEMISTRY OF STERICALLY HINDERED AROMATIC METHOXY GROUPS

Major Field: Chemistry

Biographical:

Personal Data: Born in Calambrone, Italy, September 11, 1958, the daughter of Louis C. and Paula Wysocki.

Education: Graduated from Eisenhower Senior High School, Lawton, Oklahoma, in May, 1976; received the Bachelor of Science Degree in Chemistry from Cameron University, Lawton, Oklahoma, in May, 1980; completed requirements for the Doctor of Philosophy degree at Oklahoma State University in July, 1985.

Professional Experience: Undergraduate Research Assistant, Texas Women's University, Denton, Texas, summers, 1977 and 1978; Chemist, Halliburton Services Intl., Duncan, Oklahoma, summer 1980; Skinner Fellow, Oklahoma State University, 1980-1981; Graduate Teaching Assistant, Oklahoma State University, 1980-1982; Graduate Research Assistant, United States Department of Energy, Oklahoma State University, 1982 and 1983; Conoco Summer Fellow, Oklahoma State University, 1982; Graduate Research Assistant, Gulf Research and Development Company, Oklahoma State University, 1983; Dow Chemical Summer Fellow, Oklahoma State University, 1983; Graduate Research Assistant, University Center for Energy Research, Oklahoma State University, 1984-1985. Member of Phi Lambda Upsilon, Honorary Chemical Society, and the American Chemical Society.